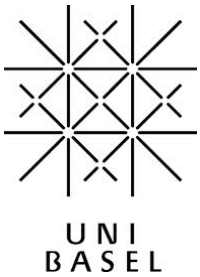

Sex dependency and genetic modulation of emotional processing and memory: a behavioural and imaging study

A cumulative dissertation

submitted to the Faculty of Psychology, University of Basel,
in partial fulfilment of the requirements for the degree of Doctor of philosophy

by

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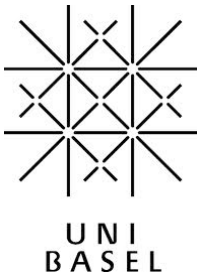

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ABSTRACT

Emotional processing and episodic memory are topics of great interest in neuroscience research. It is known that both of these two cognitive processes can be influenced by a variety of factors. The scope of this thesis is to highlight the importance and describe the role of two of these factors, namely sex and genetics. Our investigation on this topic consists of results that have been reported in five peer-reviewed publications, where methods from different disciplines like neuroimaging, psychoneuroendocrinology, and epigenetics were combined.

In order to assess sex-dependent differences in emotional processing and episodic memory, we conducted (in our first publication) behavioural and imaging analyses within a large sample of healthy young subjects. Our results point to differences between the sexes in emotional appraisal as well as setting-dependent differences in memory performance of pictorial information, which seem to be independent of each other. We additionally investigated the modulatory character of endogenous testosterone levels on emotional processing and memory (in the second publication). The results may suggest a role of testosterone in enhancing memory performance for neutral stimuli by increasing the biological salience of this information, as indicated by increased arousal ratings and amygdala reactivity to these stimuli.

To further investigate the genetic modulation of emotional processing and episodic memory we focused on the role of three genes (neurotrophic tyrosine kinase receptor type 2 (*NTRK2*), protein kinase C alpha (*PRKCA*) and brain derived neurotrophic factor (*BDNF*)). We provided (in out third publication) evidence for a role of a *NTRK2* variant in the emotion processing of positive stimuli in healthy young subjects and additionally found *NTRK2*-dependent differences in white matter measures as well as methylation levels. In reference to episodic memory, we found (in the fourth publication) that *PRKCA* plays a role in memory performance of healthy subjects and is also associated with specific symptoms of posttraumatic stress disorder (PTSD) as well as the risk to develop PTSD in genocide survivors. Finally (in the fifth publication), by combining original data with meta-analytic techniques, we found no association between a genetic variant of the *BDNF* gene and hippocampal volumes in our original data and show that the weak association in the meta-analysis is moderated by measuring techniques, publication year and sample size.

Taken together, these results support the presence of sex-dependent differences in emotional processing as well as episodic memory and emphasize the role of specific genes in these processes.

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ACKNOWLEDGMENTS

In my time as a PhD student in the lab of Professor Dominique de Quervain and Professor Andreas Papassotiropoulos I witnessed and was involved in neuroscience research of excellent quality. Since the lab's members are coming from different disciplines like molecular biology, psychology, medicine, physics and bio-informatics I had the unique and extremely valuable opportunity to acquire some knowledge from all these fields. It is an honour for me to have completed my PhD in such an outstanding research group.

I would therefore like to thank my supervisors Professor Dominique de Quervain and Professor Andreas Papassotiropoulos for their support throughout these years. Their expert advice, guidance, personal encouragement and understanding provided me with invaluable knowledge, skill and confidence for my future work in science.

I would also like to thank all my working colleagues, who supported me during these years in terms of teaching me their knowledge as well as giving me psychologically support. Some of them deserve particular mention: M.Sc. Matthias Fastenrath and Dr. David Coynel for their help with imaging analyses. Dr. Angela Heck for her introduction to genetic analyses. Finally, Dr. Vanja Vukojevic for providing me with knowledge in the field of epigenetics. The friendship with M.Sc. Matthias Fastenrath and M.Sc. Nathalie Schicktanz evolving within my PhD years was a great support.

Last but not least, I would specially like to thank my partner Dr. Manolis Sifalakis for his enormous support and patience in these years and to my parents, Hana and Jaroslav Spalek, for their support, which gave me endurance in the processes to get my PhD.

ABBREVIATIONS

AC:	adenylyl cyclase
ACC:	anterior cingulate cortex
AF:	activating factor
AMPA:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP:	adenosine triphosphate
BDNF:	brain derived neurotrophic factor
BLA:	basolateral amygdala
BOLD:	blood oxygenation level-dependent
C/EBP:	CCAAT-box-enhancer binding protein
Ca^{2+}:	calcium
CaMK II:	Ca^{2+}-calmodulin-dependent kinase II
cAMP:	cyclic adenosine monophosphate
CpG:	cytosine-guanine dinucleotide
CRE:	cAMP response element
CREB-1:	cAMP response element binding protein-1
CREB-2:	cAMP response element binding protein-2
CSF:	cerebrospinal fluid
DLPFC:	dorsolateral prefrontal cortex
DNA:	deoxyribonucleic acid
DTI:	diffusion tensor imaging
DWI:	diffusion weighted imaging
EF1α:	elongation factor 1α
EMG:	electromyography
EPI:	echo-planar imaging
ERP:	event-related potential
FA:	fractional anisotropy
fMRI:	functional magnetic resonance imaging
FSL:	fMRI of the brain software library
GSA:	gene set analysis
GWAS:	genome-wide association study
HRF:	hemodynamic response function
IAPS:	international affective picture system

ICV: intracranial volume
K^+: potassium
LTP: long-term potentiation
MAPK: mitogen-activated protein kinase
MD: mean diffusivity
mFC: medial frontal cortex
mPFC: medial prefrontal cortex
MRI: magnetic resonance imaging
MTL: medial temporal lobe
NAA: network-assisted analysis
NE: norepinephrine
NMDA: N-Methyl-D-Aspartate
NO: nitric oxide
NTRK2: neurotrophic tyrosine kinase receptor type 2
OFC: orbitofrontal cortex
PBA: pathway-based analysis
PET: positron emission tomography
PFC: prefrontal cortex
PKA: cAMP-dependent protein kinase A
PKC: protein kinase C
PKCα: protein kinase C alpha
PRKCA: protein kinase C alpha
PTSD: posttraumatic stress disorder
TRKB: tyrosine kinase receptor B
vmPFC: ventromedial prefrontal cortex

1. INTRODUCTION

Our daily life consists of perception and processing of information, and reactions in response to this information. Emotion and memory play a central role in these processes. A good portion of the information, we are daily confronted with, are of emotional content or in some cases we simply assign emotional meanings to this information. Emotions can as well describe a state we currently might be in; for example we can feel happy having past an exam or we can feel angry after quarrel. Furthermore, in patients with different psychiatric disorders the main characteristic is a dysregulation of emotions (Cole, Michel, & Teti, 1994; Kring & Sloan, 2009). Thus, it is obvious, that emotions play an essential role in our lives and it is not surprising that emotion processes including perception, processing and response are since long time a topic of great interest in research. The first theories about emotions date back to 1890 to the James-Lang-Theory. Today, we have developed a much more elaborated and extended concept about emotional perception, processing and reactions by connecting the knowledge from different research disciplines like psychology, molecular biology, genetics, epigenetics and neuroimaging, thanks to their diversity of methodologies. It is known that different neurotransmitters like serotonin, noradrenaline, adrenaline and dopamine are involved in emotional processes (Bear, Connors, & Paradiso, 2009; Lövheim, 2012; McGeer & McGeer, 1980). Alongside brain activations and structural characteristics especially in the amygdala, as well as in several other brain regions like prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula and hypothalamus are playing a central role in emotions (Dalgleish, 2004; Phan, Wager, Taylor, & Liberzon, 2004). In this thesis we focus specifically on the emotion processing stage.

On the other hand, memory, which is the ability to encode, store and retrieve information and experiences, is equally essential for our daily functioning. The best proof of the importance of our ability to form memories comes from cases where memory functions are not intact anymore like in the famous patient H.M. or in patients suffering from the Alzheimer disease or Amnesia (the loss of memory for a specific period or loss of the ability to acquire new memories). The case of H.M. as well as studies on animals and amnestic patients further lead to the differentiation of memory systems like declarative and non-declarative memory with its subsystems (Squire 2004). The work of this thesis focuses mainly on episodic memory, a sub-system of declarative memory. A major breakthrough, for the understanding of the molecular basis of memory, was Eric Kandel's work with the sea snail Aplysia Californica for which he received in 2000 the Nobel price for physiology and

medicine. On the neuronal level, research has provided evidence for the central role of the hippocampus in episodic memory (Squire & Wixted, 2011), as well as other brain regions like the cortex areas, which are initially involved in the processing of the information that is later remembered (Squire & Kandel, 2009). An important modulating factor of episodic memory performance is the perceived emotionality of the material (Roozendaal & McGaugh, 2011). Namely, information of emotionally arousing content is supposed to lead to a more elaborated processing and thus better remembering due to its salience (LaBar & Cabeza, 2006). This mechanism is evolutionary driven, since it is useful to remember threatening or rewarding situations for future behaviour. This emotional enhancement effect is partially mediated through amygdala activity (Cahill et al., 1996; McGaugh, 2004; McGaugh & Roozendaal, 2002).

Both, emotion processing and episodic memory can be influenced by several factors amongst others by sex and genetics, which are the focus of this thesis. Sex-dependent differences in emotional processing and episodic memory have been already reported in literature (emotion processing: Bradley et al., 2001; Gard & Kring, 2007; Lithari et al., 2010; episodic memory: Andreano & Cahill, 2009; Bloise & Johnson, 2007; Herlitz et al., 1997; Herlitz et al., 2013; de Frias et al., 2006). Specifically, women process especially negative material more intensively and perform in general better than men on episodic memory tasks. Concerning the genetic modulation of emotion processing and episodic memory, substantial amount of research provides evidence for an association between genes or gene clusters and these behavioural traits (Bevilacqua & Goldman, 2011; Papassotiropoulos & de Quervain, 2011). The on-going methodological progresses like the introduction of genome-wide association studies (GWAS) or pathway analysis in this discipline enable researchers to develop an understanding of the role of genes in these processes.

The aim of the present doctoral thesis consists in the contribution to a better understanding of the role of sex and genetics in emotional processing and emotional episodic memory. The intent has been to develop a more elaborated picture about these processes by combining insights from different areas (neuroimaging, psychoneuroendocrinology, genetics, and epigenetics) in investigating them. We envision that these results might provide information about the mechanisms of these processes in healthy young subjects and might add useful insights about the dysfunctions in these processes in psychiatric disorders.

The findings of this thesis have been reported in the following five publications:

1. Gender-dependent dissociation between emotional appraisal and memory: a large–scale behavioural and fMRI study.
   Spalek, K., Fastenrath, M., Ackermann, S., Auschra, B., Coynel, D., Frey, J., Gschwind, L., Hartmann, F., van der Maarel, N., Papassotiropoulos, A., de Quervain, D. J.-F., & Milnik A., in preparation (a).

2. Testosterone levels in healthy men are related to amygdala reactivity and memory performance.
   Ackermann, S.[*], Spalek, K.[*], Rasch, B., Gschwind, L., Coynel, D., Fastenrath, M., Papassotiropoulos, A., & de Quervain, D. J.-F. (2012). *Psychoneuroendocrinology*, *37*(9), 1417-1424.

3. Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects.
   Spalek, K., Coynel, D., Fastenrath, M., Freytag, V., Heck, A., Milnik, A., Vukojevic, V., de Quervain, D. J.-F., & Papassotiropoulos, A., in preparation (b).

4. PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors.
   de Quervain, D. J.-F., Kolassa, I.-T., Ackermann, S., Aerni, A., Boesiger, P., Demougin, P., Elberth, T., Ertl, V., Gschwind, L., Hadziselimovic, N., Hanser, E., Heck, A., Hieber, P., Huynh, K.-D., Klarhöfer, M., Luechinger, R., Rasch, B., Scheffler, K., Spalek, K., Stippich, C., Vogler, C., Vukojevic, V., Stetak, A., & Papassotiropoulos, A. (2012). *Proceedings of the National Academy of Sciences of the United States of America*, *109*(22), 8746-8751.

5. The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data.
   Harrisberger, F.[*], Spalek, K.[*], Smieskova, R., Schmid, A., Coynel, D., Milnik, A., Fastenrath, M., Freytag, V., Gschwind, L., Walter, A., Vogel, T., Bendfeldt, K., de Quervain, D.J.-F., Papassotiropoulos, A., & Borgwardt, S. (2014). *Neuroscience and Biobehavioral Reviews*, *42C*, 267-278.

[*] These authors contributed equally to this work.

2. THEORETICAL BACKGROUND

2.1. EMOTION

Throughout the history of science different definitions of emotion were formulated as a result of emotion theories. Historically the probably most influential theories were the James-Lange-Theory (1884) and the Cannon-Bard-Theory (1927). The James-Lange-Theory is based on the assumption that emotions are reactions to physiological changes in the body (Bear et al., 2009; Fehr & Stern, 1970). As a consequence of the criticism expressed on the James-Lange-Theory, the Cannon-Bard-Theory was developed (Bear et al., 2009; Cannon, 1987). This second theory proposes that after the emotional perception of a stimulus, the emotional experience follows and as a consequence emotions are expressed (Bear et al., 2009; Cannon, 1987). The neurological basis of emotion, especially the role of the limbic system, was introduced by theories of James Papez in 1937 (Papez, 1995) and Paul MacLean in 1949 and 1952 (MacLean, 1955). The definition of the limbic system was and partially still is under great debate (for a review see LeDoux (2003) and Lewis, Haviland-Jones, & Feldman Barrett (2008)). Over time it became clear that it is very difficult to define an emotion theory applicable to the whole pallet of emotions and that it is very unlikely that only one brain system is responsible for all these different and complex processes. As a result one of the latest emotion theories formulated by LeDoux in the 90s, focuses only on the emotion of fear and discusses the involvement of different brain structures (LeDoux, 1998).

2.1.1. EMOTION PROCESSES

The term emotion in the every day understanding implicitly includes the differentiation of basically three distinct cognitive processes: perception, processing and response (for a review see Lang, Bradley, & Cuthbert (1998) and Lewis et al. (2008)). An emotional stimulus is first perceived, then processed and finally in most cases a response to the stimulus will follow. This differentiation is not scientifically determined and thus the terms are used sometimes interchangeably. In the context of experimental studies emotions are often induced visually by means of face photographs or natural scenes. The International Affective Picture System (IAPS; Lang, Öhmann, & Vaitl, 1988) is widely used and consists of a large set of standardized, emotion evoking, colour photographs covering a wide range of semantic categories. To investigate emotion perception, subjects are usually instructed to look at the presented stimuli, while emotion processing can be assessed from participant's ratings after stimuli presentation. IAPS pictures are usually rated according to valence (ranging from

pleasant to unpleasant) and arousal (ranging from calm to excited; Lang et al., 1998). An emotion response is assumed to engage processes from three reactive systems, namely (1) language expressions, (2) physiological changes and (3) behavioural reactions (Lang et al., 1998). These response types can be recorded for example through physiological measurements (e.g. heart rate, skin conductance) or behavioural assessments (observation and quantification of reactions).

2.1.2. NEURONAL BASIS OF EMOTION

Various brain structures have been found to be involved in emotional processes, but a key role is ascribed to the amygdala (Dalgleish, 2004). Most of the established knowledge on the topic, specifically in emotion perception and processing, comes from animal, human lesion and imaging studies. Several of these studies identified increased activation during emotion processing within a neuronal network of visual, limbic, temporal-parietal, prefrontal and subcortical areas including for example the amygdala, the insula, the medial prefrontal cortex (mPFC) and the ACC (for a review see Fusar-Poli et al. (2009); Phan et al. (2004) and Phillips, Drevets, Rauch, & Lane (2003)). Taylor, Phan, Decker, & Liberzon (2003) investigated activation differences between just passively viewing as opposed to viewing and rating IAPS pictures. They observed stronger activations in the amygdala and insula during passively viewing pictures, by contrast activation in medial frontal cortex (mFC) was only present during viewing and rating of the pictures. Although some studies investigated the underlying neuronal mechanisms of emotion processes by presenting faces to subjects and others by presenting IAPS pictures, there is evidence that these stimuli lead to similar brain activation patterns (Britton, Taylor, Sudheimer, & Liberzon, 2006; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Sabatinelli et al., 2011; see figure 1A). It nevertheless is noteworthy that in some regions faces seem to lead to stronger activations than IAPS pictures (Britton et al., 2006; Hariri et al., 2002). Furthermore, valence specific activation differences have been observed in limbic structures as well as insular and ventromedial prefrontal cortex (vmPFC; Britton et al., 2006; Fusar-Poli et al., 2009; see figure 1B).

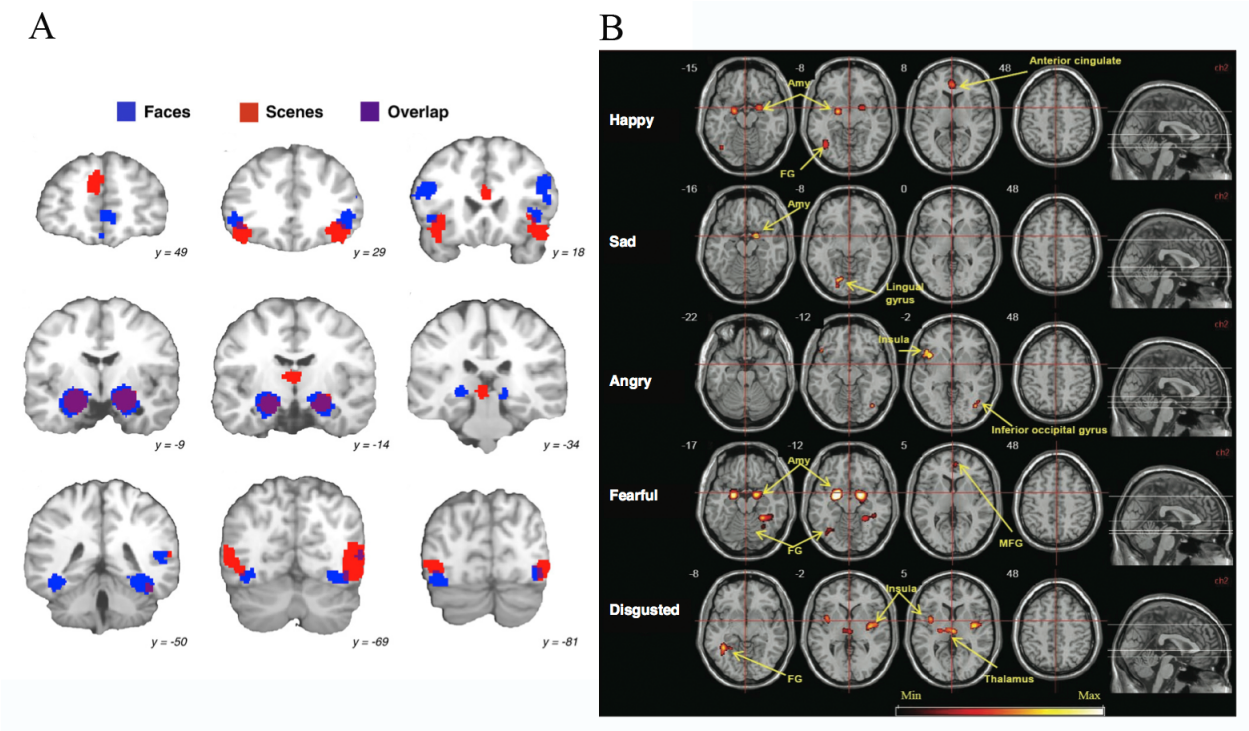

Figure 1. Brain activations during emotion perception and processing. A) Comparison of brain activation by emotional face (in blue) vs. emotional scene (in red) processing (in purple overlap of activations) from Sabatinelli et al. (2011). B) Valence-specific activation from the meta-analysis on face processing of Fusar-Poli et al. (2009).

2.2. MEMORY

What is usually understood under the term memory is the ability to encode, store and retrieve information and experiences. In scientific research, memory is understood as a very broad term incorporating many separate systems. Differentiation between these systems is based on temporal and content-related aspects as well as the involved brain structures and underlying molecular mechanisms.

2.2.1. MEMORY SYSTEMS

The temporal classification divides memory into short- and long-term memory systems (Bear et al., 2009; Squire, 1986). Short-term memory is further divided into immediate and working memory. Immediate memory encompasses the actively kept information since the beginning of information processing, which is in the focus of attention. Thus, its capacity is very limited (7 ± 2 items) and if information is not repeated, it is kept up for less than 30 seconds (Squire & Kandel, 2009). If contents from immediate memory are repeated and

edited, thus actively kept in mind for several minutes this is referred to as working memory (Squire & Kandel, 2009). Some of the information coming either from short-term memory systems or directly as input, independently of short-term memory, reaches the long-term memory (Bear et al., 2009). Long-term memory encompasses memories lasting for hours, weeks, months or even a whole life-time and is divided into two main sub-systems based on the content and consciousness: the declarative or explicit memory and the non-declarative or implicit memory (for an overview see figure 2; Bear et al., 2009; Squire, 1986, 1987; Squire & Zola, 1996; Squire, 2004).

Declarative memory is defined as the conscious recall of facts and events. More specifically, memory about facts, like the knowledge that the capital of Switzerland is Bern, is referred to as semantic memory and does not necessarily include the information about when and where this information was acquired (Bear et al., 2009; Squire, 1986; Squire & Zola, 1998; Squire, 2004). Whereas the memory about events, e.g. yesterday evening I had a nice dinner at the new restaurant in town, is called episodic memory and usually contains the information about where and when the event occurred (Bear et al., 2009; Squire, 1986; Squire & Zola, 1998; Squire, 2004). In general, declarative memory consists of four processing stages: encoding, consolidation, recall and forgetting (Squire & Kandel, 2009). First the information is processed (encoding) and then it is saved (consolidation). If needed the information is reproduced (recall) and maybe with the course of time lost (forgetting).

The non-declarative memory is activated without our conscious awareness and is rather expressed through performance (Bear et al., 2009; Squire, 1987; Squire & Zola, 1996; Squire, 2004). It is further subdivided into categories like procedural memory (memory for skills e.g. biking), priming (facilitation of stimuli identification due to previous exposure) as well as perceptual learning (ability to discriminate perceptual attributes due to previous exposure), simple classical conditioning (memory about a relationship of two stimuli), and non-associative learning including habituation (reduced reaction to a neutral stimulus because of repeated exposure), and sensitization (strong reaction to a otherwise neutral stimulus based on exposure to a previous aversive stimulus; Bear et al., 2009; Squire, 1987; Squire & Zola, 1996; Squire, 2004; Squire & Kandel, 2009). Non-declarative memory is less flexible than declarative memory in the sense that the acquired knowledge is not available to systems not involved in the initial learning (Squire & Zola, 1996).

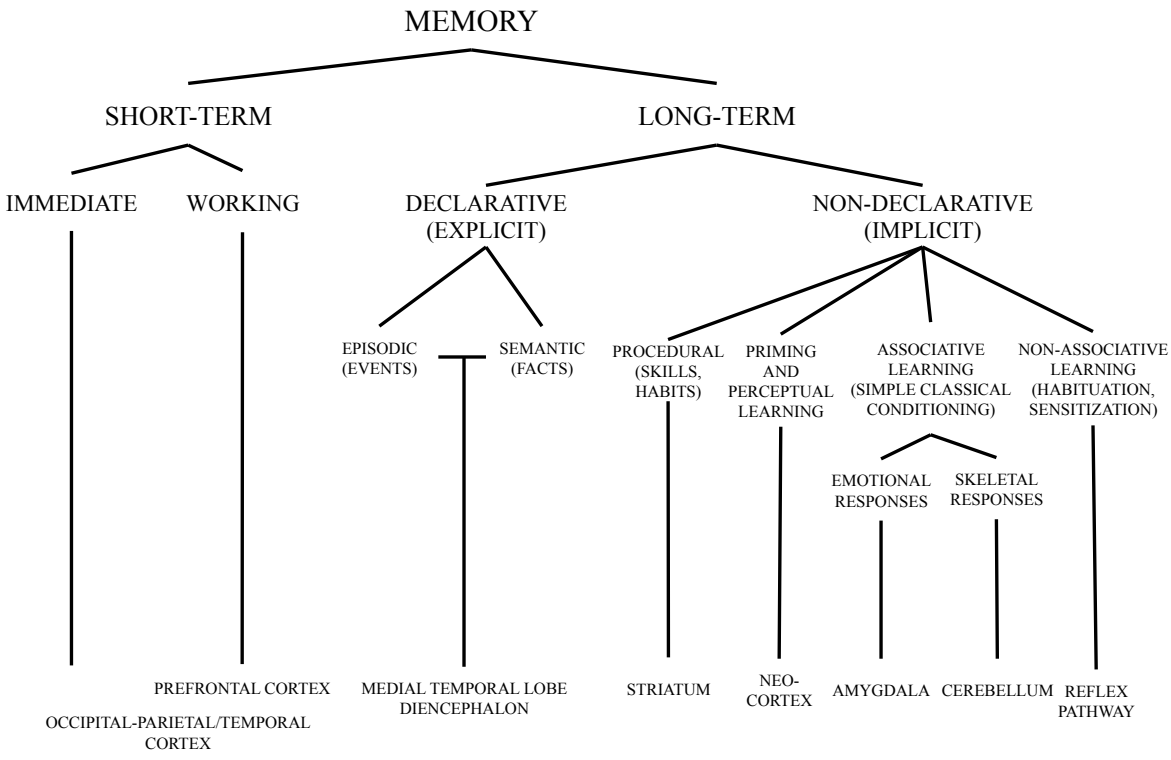

Figure 2. Overview of memory systems adapted from Squire (2004).

2.2.2. NEURONAL BASIS OF MEMORY

Several brain structures are involved in the functioning of the different memory systems (for an overview see figure 2). Immediate memory was observed to show a stimulus-specific activation, namely activations in occipital to temporal cortex (ventral stream) during the processing of form and quality of a stimulus and in occipital to parietal cortex (dorsal stream) when processing the location of a stimulus (Hautzel et al., 2002; Squire & Kandel, 2009). Working memory involves in addition to this occipital-temporal-parietal network the prefrontal cortex (PFC; Bear et al., 2009; Squire & Kandel, 2009). Independent of the type of stimuli (e.g. verbal, object, spatial information) the same areas within the PFC seem to be involved in working memory (Hautzel et al., 2002). The PFC is suggested to exert a top-down control on the other brain regions activated by the processed information, in the sense of maintaining their activation (Gazzaley & Nobre, 2012; Squire & Kandel, 2009).

In long-term memory, according to the model of Squire (2004), the regions involved in the two types of declarative memory are supposed to be the same, whereas brain structures important for non-declarative memory are very heterogeneous. Central structures for semantic

and episodic memory are the medial temporal lobe (MTL) and the diencephalon (Bear et al., 2009; Squire, 2004; Squire & Wixted, 2011; Squire & Kandel, 2009). The medial temporal lobe encompasses different structures like the amygdala, the hippocampus and the surrounding cortex (parahippocampal, perirhinal and entorhinal cortex). From animal studies and studies on patients with lesions it emerged that especially the hippocampus and its surrounding cortex play an essential role in declarative memory (Bear et al., 2009; Squire, 1992; Squire & Wixted, 2011; Squire & Kandel, 2009). Furthermore, the diencephalon specifically the anterior and dorsal medial nuclei of the thalamus, mammillary bodies in the hypothalamus, and mammillo-thalamic tract, are central for functional declarative memory (Bear et al., 2009; Squire & Wixted, 2011). This is explainable by their connection to the MTL (Bear et al., 2009; Squire & Wixted, 2011). The most important output of the hippocampus is an axon bundle, so-called fornix. Most of its axons lead to the mammillary bodies, and its neurons project to the anterior thalamic nuclei. In general, the role of the MTL seems to be restricted time wise (Squire & Kandel, 2009). In the initial stage of memory formation several cortical structures as well as the MTL are involved. In the time after memory storage, the information gets reorganized and stabilized, not depending on the hippocampus any more. When this information is recalled the same cortical regions, which were processing the information, are reactivated depending gradually less on the MTL structures and more on the neocortex (Squire & Kandel, 2009).

On the other hand, non-declarative memory depends, based on the specific memory sub-system, on completely distinct brain structures. Procedural memory involves mainly a part of the basal ganglia, the striatum (nucleus caudatus and putamen; Bear et al., 2009; Squire, 1992; Squire, 2004). The striatum receives information from the frontal and parietal cortex and its output is transferred to some thalamic nuclei as well as cortical regions involved in the motoric response (Bear et al., 2009). In priming and perceptual learning the neocortex is supposed to play a central role (Buckner & Koutstaal, 1998; Schacter & Buckner, 1998; Squire, 1992, 2004). The specific neuronal location can vary with stimulus characteristics (Schacter & Buckner, 1998) and for perceptual learning is strongly task- as well as training-specific (Squire & Kandel, 2009). Usually decreased activations in regions involved in the prior processing of the stimulus are observed, pointing to a more efficient processing after exposure to the stimulus (Buckner & Koutstaal, 1998; Schacter & Buckner, 1998). The associative learning such as the classical conditioning, involves the amygdala for emotional responses and the cerebellum for skeletal responses, while the non-associative learning

including habituation and sensitization is based on reflex pathways (Squire, 1992; Squire, 2004; Squire & Kandel, 2009).

2.2.3. MOLECULAR BASIS OF MEMORY

The investigation of molecular processes underlying short-term and long-term memory formation is mainly based on the work of Kandel and colleagues using the sea snail Aplysia Californica as a model organism (Kandel, 2001; Kandel, 2012; Squire & Kandel, 2009). Specifically, the animals gill withdrawal reflex was used to model three different forms of implicit memory such as habituation, sensitization and conditioning (Kandel, 2001; Kandel, 2012). Whereas major differences in the molecular mechanisms appear between short-term and long-term memory, similar mechanisms are implied in implicit and explicit memory (Barco, Bailey, & Kandel, 2006; Kandel, 2001; Kandel, 2012). Above all, most of these molecular mechanisms investigated in the Aplysia seem to be conserved from invertebrates to mammals (Clapp, Hamm, Kirk, & Teyler, 2012; Kandel, 2001; Kandel, 2012).

Short-term memory consists in the modification of pre-existing proteins as well as synaptic connections (Kandel, 2001; Kandel, 2012; Mayford, Siegelbaum, & Kandel, 2012; Squire & Kandel, 2009). In the short-term phase of sensitization, produced by a single tail shock, serotonin is released, binds to a serotonin receptor and activates a molecular signalling cascade. Frist, the adenylyl cyclase (AC) enzyme is activated and converts adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP). This in turn, activates the cAMP-dependent protein kinase A (PKA) by binding to the regulatory subunits of PKA (see figure 3, spindles) and thus mobilizes the catalytic or active subunits (see figure 3, ovals). These active subunits increase neurotransmitter release by (1) closing the potassium (K^+) channels hence increasing the calcium (Ca^{2+})-influx and by (2) directly acting on proteins in a Ca^{2+}-independent manner involved in mobilization, fusion and release of neurotransmitter vesicles (for overview see figure 3). On the other hand, the long-term phase of sensitization implies synaptic changes such as activation of gene expression, protein synthesis and formation of new connections (Bailey & Kandel, 2008; Kandel, 2001; Kandel, 2012; Mayford et al., 2012; Squire & Kandel, 2009). In the case of repeated tail shocks leading to long-term sensitization, cAMP concentration stays elevated for a longer time period and the catalytic subunits of PKA activate mitogen-activated protein kinase (MAPK). Both the catalytic subunits and MAPK are translocated to the nucleus, where PKA activates cAMP response element binding protein-1 (CREB-1) and MAPK deactivates the CREB-1 suppressor cAMP response element binding protein-2 (CREB-2). By binding to the cAMP

response element (CRE) in the promoter of target genes, CREB-1 activates several genes including ubiquitin hydrolase. This results in persistent activity of PKA, and the transcription factor CCAAT-box-enhancer binding protein (C/EBP), which in combination with the activating factor (AF) activates downstream genes such as elongation factor 1α (EF1α) leading to growth of new synaptic connections (for overview see figure 3; Kandel, 2001; Kandel, 2012; Mayford et al., 2012; Squire & Kandel, 2009).

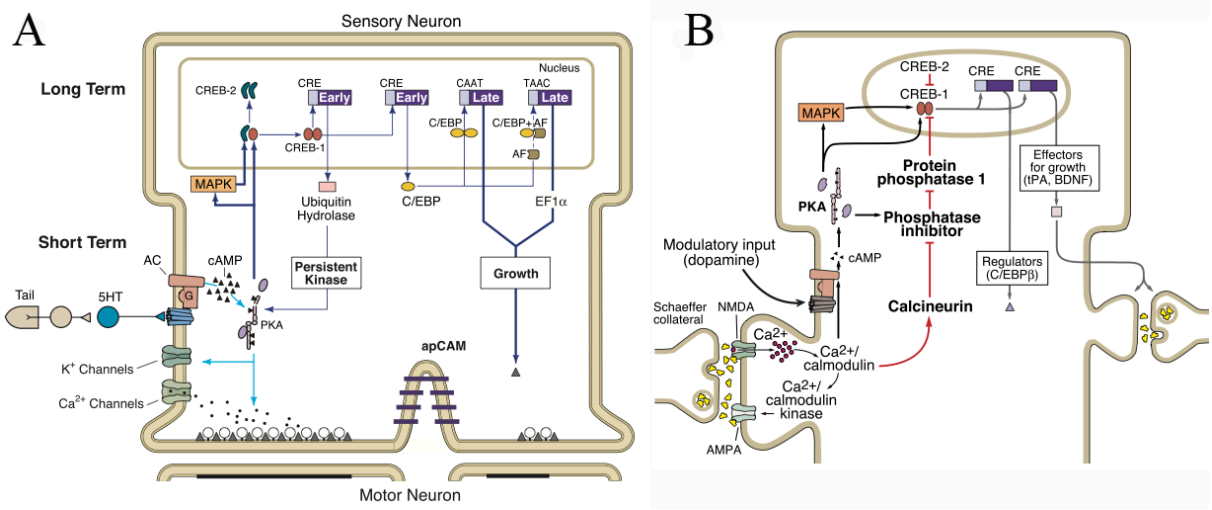

Figure 3. Molecular mechanisms of short- and long-term memory in A) the Aplysia during sensitization and in B) the hippocampus, specifically in the Schaeffer collateral, of mice (from Kandel (2001)).

Explicit memory such as implicit memory has a short-term phase not involving protein synthesis and a long-term phase requiring protein synthesis. In 1972, Bliss and Lomo discovered the concept of long-term potentiation (LTP; Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973), which is defined as activity-dependent plasticity resulting in a persistent enhancement of synaptic transmission and divided into early- and late-phase LTP (Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973; Malenka & Nicoll, 1999). Given the central role of the hippocampus in episodic memory (Squire & Wixted, 2011), the first LTP observation in the hippocampus (Bliss & Collingridge, 1993; Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973), and the inhibition of hippocampus-dependent memory by LTP-blockade using an N-Methyl-D-Aspartate (NMDA)-inhibitor (Ekstrom, Meltzer, McNaughton, & Barnes, 2001; Kandel, 2001; Shapiro, 2001), evidence was provided for the involvement of LTP and NMDA-receptors in explicit memory. The early-phase of LTP requires different signalling than the short-term phase of implicit memory (for a overview see figure 3; Barco et al., 2006). As depicted by example in figure 3B, in the Schaeffer collateral

in the hippocampus, single high-frequent stimulation activates NMDA-receptors through binding of glutamate and removing the magnesium-ion, which is blocking the channel. Hence, Ca^{2+}-influx is enabled into the postsynaptic cell. The Ca^{2+} binds to Ca^{2+}/calmodulin and activates three protein kinases: Ca^{2+}-calmodulin-dependent kinase II (CaMK II), the protein kinase C (PKC) and the tyrosine kinase (not all are depicted in figure 3). CaMK II not only phosphorylates the NMDA-receptors, thus increasing their responsivity to glutamate, but also triggers the integration of new α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptors into the postsynaptic membrane (Lisman, Schulman, & Cline, 2002). Since NMDA-receptors are not, as AMPA-receptors, active during routine synaptic transmission, the conductance change of AMPA-receptors and the integration of new AMPA-receptors could explain how the LTP is stabilized and maintained (Huganir & Nicoll, 2013; Squire & Kandel, 2009). The late-phase of LTP is based on the same signalling pathway as the long-term phase of implicit memory. After repeated stimulation by action potentials the Ca^{2+}-influx additionally activates AC and consequently activates the cAMP, PKA, MAPK and CREB signalling pathway, as well as synaptic growth. Furthermore, modulatory inputs like dopamine can modulate AC activation. Phosphatases such as calcineurin can influence the balance between protein phosphorylation-dephosphorylation and through this can constrain the late-phase of LTP and consequently memory (Malleret et al., 2001; Zeng et al., 2001). An additional mechanism contributing to LTP is an increase of neurotransmitter release in the presynaptic cell, which is suggested to be modulated by a retrograde mechanism from the postsynaptic cell as par example nitric oxide (NO; Hardingham, Dachtler, & Fox, 2013; Squire & Kandel, 2009). Importantly, the mechanism of late-phase LTP does not develop in any synapse, but only in synapses that were activated before and thus received a temporally limited synaptic tag, therefore referring to this process as synaptic tagging or capturing (Frey & Morris, 1997; Martin & Kosik, 2002; Redondo & Morris, 2011; Squire & Kandel, 2009).

2.3. MEMORY MODULATION THROUGH EMOTION

It is well known that emotional information is better remembered than neutral one; a condition known as the emotional memory enhancement effect (McGaugh, 2003). Enhanced memory for emotional information is essential in evolutionary terms, since remembering dangerous and favourable situations is pivotal for survival and proliferation. Specifically the more arousing information is perceived, the more likely it will be remembered (LaBar &

Cabeza, 2006). Furthermore, the emotional memory enhancement effect is partially mediated through noradrenergic activation of the basolateral amygdala (BLA; Cahill, Haier, Fallon, Alkire, Tang, Keator, Wu, & McGaugh, 1996; McGaugh, 2002, 2004), upon release of stress hormones like glucocorticoids and epinephrine (Roozendaal & McGaugh, 2011). Finally, the influence of BLA upon other brain structures like the hippocampus, caudate nucleus, nucleus accumbens and several cortical regions is crucial in the memory enhancement effect of emotion (for an overview see figure 4; McGaugh, 2002; Phelps, 2004; Roozendaal & McGaugh, 2011).

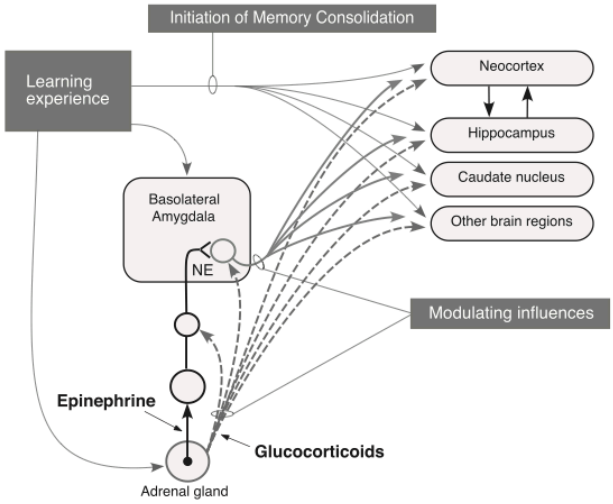

Figure 4. Schematic representation of the components of the emotional memory enhancement effect (NE = norepinephrine; from Roozendaal & McGaugh (2011)).

There is evidence that the BLA modulates hippocampal LTP (Roozendaal & McGaugh, 2011). Specifically stimulation of BLA enhances LTP in the dentate gyrus of the hippocampus (Roozendaal & McGaugh, 2011). This reinforcement of hippocampal LTP is also embedded in the context of the emotional tagging, where it is suggested that an arousing emotional event activates a cascade of processes, hence leading to the supply of plasticity-related proteins to tagged synapses and thus can convert early-phase LTP to late-phase LTP (Bergado, Lucas, & Richter-Levin, 2011; McReynolds & McIntyre, 2012).

Several studies provide evidence for an influence of emotional arousal not just in the consolidation stage, but already in the encoding stage (for review see Hamann (2001)), which means, the emotional memory enhancement effect is observed already a few minutes after stimulus presentation as well as when emotional and neutral stimuli alternate rapidly (within

seconds) underlining the emotional specificity of this effect (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999; de Quervain et al., 2007).

2.4. MODULATING FACTORS OF EMOTIONAL PROCESSING AND EPISODIC MEMORY

Both processes which are in the focus of this thesis, namely emotional processing and episodic memory are very complex traits and thus can be additionally influenced by a broad spectrum of other modulating factors like hormones, sex, genetics, environmental factors as well as interactions between these factors. This thesis specifically has explored two of these factors being sex and genetics.

2.4.1. SEX

In what concerns emotional processing there is evidence that men and women react differently on emotional material (Gard & Kring, 2007). Particularly for aversive material, it was shown that women rate the emotional stimuli as more arousing in comparison to men and in addition react stronger to aversive pictures measured in physiological responses like event-related potentials (ERPs), electromyography (EMG), and startle response (Bradley et al., 2001; Gard & Kring, 2007; Lithari et al., 2010). These sex differences might in part be due to differences in hormonal levels of gonadal hormones, vasopressin, and oxytocin (Andreano & Cahill, 2009; Ertman, Andreano, & Cahill, 2011; Honk & Schutter, 2007; Kret & Gelder, 2012; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Uzefovsky, Shalev, Israel, Knafo, & Ebstein, 2012) as well as several environmental factors like gender-stereotypic socialization and socio-moral explanation (Fischer, Rodriguez Mosquera, Vianen, & Manstead, 2004; Mathieson & Banerjee, 2011). These behavioural sex-dependent differences in emotion processing are as well visible at a neuronal level (for a review see Andreano & Cahill (2009) and Stevens & Hamann (2012)). Specifically, stronger brain activations in women are observed during the processing of negative emotions, whereas men show increased activations when processing positive emotions (for an overview see figure 5; Stevens & Hamann, 2012).

Regarding episodic memory performance there is evidence that females outperform males (Andreano & Cahill, 2009; Bloise & Johnson, 2007; Herlitz, Nilsson, & Bäckman, 1997; Herlitz, Reuterskiöld, Lovén, Thilers, & Rehnman, 2013; de Frias, Nilsson, & Herlitz,

2006). This female's advantage can already be observed in childhood and puberty (Herlitz et al., 2013; Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997) and is stable over time in adulthood and older age (de Frias, Nilsson, & Herlitz, 2006). In a recent study of (Young, Bellgowan, Bodurka, & Drevets, 2013) higher activations in dorsolateral prefrontal cortex (DLPFC), dorsal anterior insula, and precuneus were observed in women compared to men during the recall of autobiographic memories.

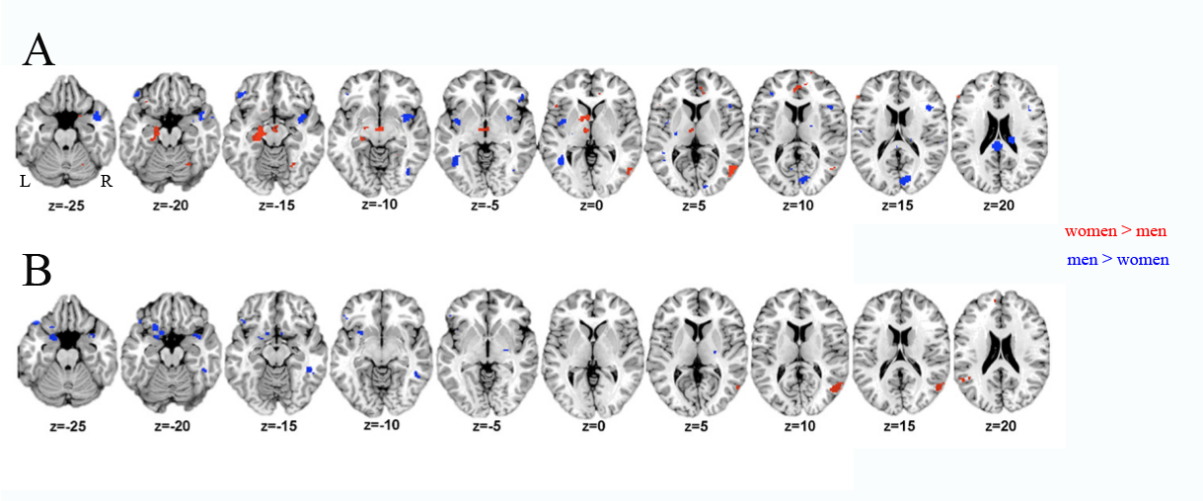

Figure 5. Sex-dependent brain activation differences during emotion processing A) of negative emotions and B) of positive emotions (from Stevens & Hamann (2012)).

There is evidence that also for emotional memory women show enhanced performance compared to men (Andreano & Cahill, 2009). Several studies observe sex-dependent brain activation differences specifically in the amygdala in subsequent emotional memory contrasts (Andreano & Cahill, 2009; Cahill, 2003; Hamann, 2005). There is however a lack of studies investigating whole-brain wide sex-dependent activation differences in emotional memory. In general, it has to be considered that the evidence for better performance of females compared to males is mostly based on episodic memory recall tasks of life events (Andreano & Cahill 2009).

Taken together, it is unclear so far if the behavioural differences between the sexes in emotional processing and episodic memory, specifically emotional memory, are two independent processes or linked to each other. More specifically, female's stronger perception of emotionally arousing information could lead to stronger encoding thereby inducing an advantage in episodic emotional memory performance. In the publication "Gender-dependent dissociation between emotional appraisal and memory: A large–scale behavioural and fMRI study" (Spalek et al., in preparation (a)) we investigated the relationship between sex-

dependent differences in emotional processing and emotional memory performance as well as the underlying neuronal patterns. Additionally, it is known that testosterone can exert its influence through binding to androgen and estradiol receptors in brain regions like the amygdala and the hippocampus, which are involved in emotional processing as well as emotional memory (Abdelgadir, Roselli, Choate, & Resko, 1999; Beyenburg et al., 2000; Kritzer, 2004; Roselli, Klosterman, & Resko, 2001; Sarkey, Azcoitia, Garcia-Segura, Garcia-Ovejero, & DonCarlos, 2008; Sarrieau et al., 1990; Simerly, Chang, Muramatsu, & Swanson, 1990). Several studies found an association between testosterone and affective behaviour (for a review see van Wingen, Ossewaarde, Bäckström, Hermans, & Fernández (2011)), as well as amygdala activation in response to biologically salient stimuli (Derntl et al., 2009; Hermans, Ramsey, & van Honk, 2008; Stanton, Wirth, Waugh, & Schultheiss, 2009) and memory performance (Barrett-Connor, Goodman-Gruen, & Patay, 1999; Cherrier et al., 2005; Cherrier et al., 2002; Fonda, Bertrand, O'Donnell, Longcope, & McKinlay, 2005; Hogervorst, Matthews, & Brayne, 2010; Moffat et al., 2002; Perry et al., 2001; Wolf & Kirschbaum, 2002; Yonker, Eriksson, Nilsson, & Herlitz, 2006; Young, Neiss, Samuels, Roselli, & Janowsky, 2010). But it is not clear if testosterone might have an impact on memory perfromance by modulating amygdala reactivity during processing. Thus we aimed at analysing this possibility in our publication "Testosterone levels in healthy men are related to amygdala reactivity and memory performance" (Ackermann et al., 2012).

2.4.2. GENETICS

Emotion (Bevilacqua & Goldman, 2011) and episodic memory (Papassotiropoulos & de Quervain, 2011) as well as emotional episodic memory (Todd, Palombo, Levine, & Anderson, 2011) are complex polygenetic behavioural traits, influenced by genetic and environmental factors as well as by gene-environment interactions. These traits have substantial heritability estimates varying between 30% - 60% (Bevilacqua & Goldman, 2011; Papassotiropoulos & de Quervain, 2011). Given the broadness of the genetically driven influence on these cognitive traits, the focus of this thesis was on the role of three specific genes described in the following.

First, the *NTRK2* gene, also known as tyrosine kinase receptor B (*TRKB*), is associated in several studies with various psychiatric disorders like depression, schizophrenia, addiction, eating and anxiety disorders (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta, You, Gupta, Klistorner, & Graham, 2013; Hauger, Risbrough, Oakley, Olivares-Reyes, & Dautzenberg, 2009; Hill, 2012; Kohli et al., 2010; Mahan & Ressler, 2012;

Marsden, 2013). Given that the dysregulation of emotional processes is a common characteristic of many psychiatric disorders (Cole, Michel, & Teti, 1994; Kring & Sloan, 2009) and the evidence for the involvement of *NTRK2* in these disorders, it can be hypothesized that *NTRK2* is genetically associated with emotion processing. Since there is a lack of studies examining the role of *NTRK2* in emotional processing in healthy subjects, we investigated this aspect in the publication "Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects" (Spalek et al., in preparation (b)).

Second, following the considerable evidence for an important role of protein kinases like PKA, PKC, CaMK II and MAPK in memory formation from animal and human studies (Sun & Alkon, 2014; Xu, Liu, & Alkon, 2014; de Quervain & Papassotiropoulos, 2006), as well as emotional memory formation based only on animal studies (McGaugh, 2000; Rodrigues, Schafe, & LeDoux, 2004), we investigated the role of genes encoding for protein kinases in human emotional memory in the publication "PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors" (de Quervain et al., 2012).

Finally, BDNF, encoded by the *BDNF* gene, is suggested to be involved in synaptic plasticity (Bliss & Cooke, 2011; Lu, Christian, & Lu, 2008; Martin & Kosik, 2002). BDNF is highly expressed in the hippocampus (Binder & Scharfman, 2004; Wetmore, Ernfors, Persson, & Olson, 1990), a central brain structure for learning and memory (Squire & Wixted, 2011). Additionally, BDNF has been shown to play a role in learning and memory processes (Baj, Carlino, Gardossi, & Tongiorgi, 2013; Cunha, Brambilla, & Thomas, 2010). Thus, many studies investigated the association of *BDNF* gene with hippocampal volumes, but so far results are very inconsistent. In the publication "The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data" (Harrisberger et al., 2014) we investigated the association of a genetic variant of the *BDNF* gene (rs6265) and hippocampal volumes. With the aim to increase the statistical power of our results, we conducted a meta-analysis and combined it with our own study data. We additionally addressed the influence of potential moderators such as measuring technique, magnetic field strength, age, gender, ethnicity, Val/Met ratio, sample size, quality rating, hippocampal volumes normalized to intracranial volume (ICV), and publication year.

3. METHODS

3.1. NEUROIMAGING

In the last years, imaging techniques have found extensive applications in neuroscience research. Imaging techniques based on magnetic resonance imaging (MRI) like functional magnetic resonance imaging (fMRI), diffusion weighted imaging (DWI), resting state and structural measures are very commonly used ones next to positron emission tomography (PET). The results of this thesis are based on fMRI, diffusion tensor imaging (DTI) and structural measurements.

fMRI is used for measuring neuronal activity by recording changes in cerebral blood flow. The concept of fMRI is founded upon the blood oxygenation level-dependent (BOLD) response, which basically states that the measured MR signal changes in dependence of the ratio of oxygenated vs. deoxygenated blood, given the different magnetic properties the blood has in these two states. It is assumed that oxygenated blood is delivered to activated brain regions in order to enable the increased neuronal activity, in form of the so-called hemodynamic response function (HRF). The HRF can vary across subjects, between brain regions and between tasks (Waugh, Hamilton, & Gotlib, 2010). Compared to other imaging techniques fMRI has many advantages such as that it is non-invasive, it has a relatively short acquisition time, and good spatial as well as reasonable temporal resolution. Despite the often mentioned limitation that the BOLD response is an indirect measure, a study of Logothetis, Pauls, Augath, Trinath, & Oeltermann (2001) provides evidence for the BOLD signal reflecting the input and processing of neuronal information in a specific area. Other limitations of fMRI are that there is no distinction between excitatory and inhibitory connections, further the signal might be influenced by large vessels (even when they are located far from the activation site), and it has to be considered that one brain voxel contains many different physiological components (e.g. around five million neurons, $2e^{10}$ to $5e^{10}$ synapses, around 220 km of axons; Logothetis, 2008).

DTI is a subcategory of DWI and is usually used to measure the diffusion of water as a function of spatial location (Johansen-Berg & Behrens, 2009). The functional principle that enables DTI is that water molecules tend to diffuse more freely along the axon fibres, thus the measure of water diffusion relates to axonal orientation (Johansen-Berg & Behrens, 2009). In gray matter water diffusion is largely independent of tissue orientation (isotropic), whereas in white matter diffusion is mostly tissue orientation-dependent (anisotropic; Johansen-Berg & Behrens, 2009). Two commonly used measures in DTI are (1) fractional anisotropy (FA), which is a measure of the directional dependence of diffusion (Basser, 1995) and reflects fibre

density as well as coherence within a voxel (Beaulieu, 2002), and (2) mean diffusivity (MD), which reflects the magnitude of water diffusion within a voxel and depends on the density of physical obstructions like membranes and the distribution of water molecules between different cellular compartments (Beaulieu, 2002; Sen & Basser, 2005). There are some limitations of DTI, which have to be considered like the inferential character of resulting white matter properties, possible failure of connection identification, further displayed white matter connections do not have to be functional (representation of anatomy not function), and its sensitivity to artefacts introduced through reduced spatial resolution (usually due to the commonly applied echo-planar imaging technique (EPI)), subject motion and periodic ventricular pulsations with each heart beat (Alger, 2012).

Structural measures can be used to assess brain volume differences among subjects (for a review see Caviness, Lange, Makris, Herbert, & Kennedy (1999)). For the analysis volumetric data are segmented into cortical and subcortical structures as well as cerebrospinal fluid (CSF). Segmentation can be done either manually or automatically. Even though manual segmentation is generally considered as the gold standard due to the precise delineation of anatomical structures, the increasing sample size in imaging studies renders the process of manual segmentation less practicable, as it is both costly and time consuming. For automated segmentation there are different tools available like FreeSurfer or fMRI of the brain software library (FSL).

Importantly, in all these three types of imaging measurements the brain is divided into thousands of voxels, which makes a correction for multiple testing necessary in analysis. Additionally, if not main interest of the imaging analysis controlling for sex, age and in the case of structural data for ICV will allow to address their potential influence.

3.2. PSYCHONEUROENDOCRINOLOGY

The field of psychoneuroendocrinology incorporates the investigation of the association between psychological concepts with neuronal correlates and the endocrine system. To examine the role of the endocrine system in this interplay different approaches are used such as measuring hormone levels from blood or saliva as well as pharmacological manipulation by administering the hormone being investigated. When performing statistical analyses of endocrine measures, it is important to take into account possible moderating factors like circadian rhythmicity, sex, as well as age. Research applying the psychoneuroendocrinological approach found a wide application.

Numerous studies focused specifically on the psychoneuroendocrinological aspects of emotional processing, memory as well as episodic memory, investigating for instance the role of cortisol (Ackermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2013; Het, Ramlow, & Wolf, 2005; Wolf, Kuhlmann, Buss, Hellhammer, & Kirschbaum, 2004; van Ast et al., 2013), estrogen (Gasbarri, Tavares, Rodrigues, Tomaz, & Pompili, 2012; Pompili, Arnone, & Gasbarri, 2012) and testosterone (Thilers, Macdonald, & Herlitz, 2006; van Wingen et al., 2011).

3.3. GENETIC ANALYSIS

In general, when performing genetic analyses it is crucial that the investigated trait has substantial heritability rates. Given this prerequisite basically two different genetic approaches can be used to analyse the data, namely linkage and association studies (Papassotiropoulos & de Quervain, 2011). Linkage studies are usually performed in pedigrees in the context of a disease that represents the trait of interest. They aim at identifying a genetic variation, at an unknown trait locus, which is associated with the disease, by taking advantage of the linkage between the trait locus and a marker with known location. If the trait locus is in linkage disequilibrium with the marker locus, then the alleles of both loci are very likely to be inherited together (cosegregation during meiosis). Various methods can be used to identify the trait-related genetic variant like positional cloning, fine-mapping and in-depth resequencing (Neale, Ferreira, Medland, & Posthuma, 2008; Papassotiropoulos & de Quervain, 2011). On the other hand, association studies compare the genotype frequencies of common genetic polymorphisms between groups of unrelated (case-control design) or related (family-based design) individuals, and are well suited for application to quantitative traits like for instance episodic memory (Neale et al., 2008; Papassotiropoulos & de Quervain, 2011). Within the class of association studies further two distinct study types are distinguished, namely candidate gene studies and GWAS. Candidate gene studies are usually applied when there is prior knowledge about the gene's (or several genes) biological relevance for the trait or disease of interest. This approach is hypothesis driven and very focused, but bias afflicted and prevents the identification of novel genes. Thus, if the aim is to identify a novel gene (or several genes), which is (are) associated with a trait or a disease, GWAS are the method of choice. In a GWAS analysis, millions of genetic variants located at different position on the entire genome are tested for an association with the trait or disease of interest (Papassotiropoulos & de Quervain, 2011). Although all these approaches are extensively used, a considerable amount of the heritability of complex phenotypes like episodic memory

or emotion is still unexplained, and therefore has been termed as “missing heritability” (Papassotiropoulos & de Quervain, 2011). In an effort to improve this unsatisfactory situation, approaches focusing on gene-gene interactions, gene set analysis (GSA) and genetic networks are becoming more popular and elaborated. Analysis addressing gene-gene interactions, for example in the sense of statistical epistasis, are used to investigate interactions between loci of genes (for a review see Cordell (2009)). GSA like for instance pathway-based analysis (PBA) goes a step further by examining the association of a set of genes, which are biologically related in the sense of having similar function (thus being summarized as a pathway), with the given disease or trait (for a review see Holmans (2010) and Wang, Li, & Hakonarson (2010)). Genetic analysis applying a network approach like network-assisted analysis (NAA) investigates as well the association between gene sets and phenotype, but is not using pre-defined gene sets like in the case of PBA, instead defines gene sets based on sub-network search algorithms (for a review see Jia & Zhao (2014)).

3.4. EPIGENETIC ANALYSIS

The field of epigenetics investigates processes in cells, which take place above the level of genetics, namely processes that alter gene function without changing the deoxyribonucleic acid (DNA) sequence (Fazzari & Greally, 2010; Sweatt, 2013). In the recent years epigenetics have received a lot of attention in research and a broad range of applications in several domains. Within this thesis the focus is restricted to epigenetics in neuroscience, also termed as neuroepigenetics by Sweatt (2013). In his review Sweatt (2013) divides the major epigenetic molecular mechanisms into eight different categories. DNA cytosine methylation, a subcategory of the covalent DNA modification category, is one of the most studied epigenetic mechanisms given its strong regulatory influence on gene transcription (Fazzari & Greally, 2010; Sweatt, 2013) and is within the focus of this thesis. DNA methylation seems to occur preferentially at cytosine-guanine dinucleotide (CpG) DNA sequences, so called CpG sites, but according to recent findings can occur as well at non-CpG sites (Fazzari & Greally, 2010; Sweatt, 2013). Various statistical methods, already used in analysis of other large data sets, are applied as well in methylation analysis (for a review see Fazzari & Greally (2010)). Methodological approaches for statistical analyses of methylation data are still emerging. Different normalization, pre- and post-processing strategies for large-scale methylation data (in the case of whole-genome methylation data) are getting introduced. For a methodological approach proposal see Milnik et al. (in preparation).

4. ORIGINAL RESEARCH PAPERS

4.1. GENDER-DEPENDENT DISSOCIATION BETWEEN EMOTIONAL APPRAISAL AND MEMORY: A LARGE–SCALE BEHAVIOURAL AND FMRI STUDY

Spalek, K., Fastenrath, M., Ackermann, S., Auschra, B., Coynel, D., Frey, J., Gschwind, L., Hartmann, F., van der Maarel, N., Papassotiropoulos, A., de Quervain, D. J.-F., & Milnik, A., in preparation (a).

Title: Gender-dependent dissociation between emotional appraisal and memory: A large–scale behavioural and fMRI study.

Abbreviated title: Gender study emotional appraisal and memory

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2 The authors declare no competing financial interests.

3 Keywords: sex differences, memory, emotional memory, valence, arousal, picture task, word

4 task

Abstract (Max. 250)

Extensive evidence indicates that females outperform males in many episodic memory tasks, including remembering pictures. Furthermore, there is evidence that women evaluate emotional stimuli as more arousing than men. Because emotional arousal is known to facilitate memory storage, women's memory advantage might be due to their higher emotional perception. Here, we describe behavioural data from 3'398 healthy young subjects, who performed a picture memory task. Additionally, we analysed the functional magnetic resonance imaging (fMRI) data from $N_{max} = 696$ subjects. The behavioural results showed that females evaluate negative ($p_{arousal} < 10^{-16}$) and positive ($p_{arousal} = 2x10^{-4}$), but not neutral pictures, as emotionally more arousing than men. In the free recall test, females outperformed males not only in positive ($p < 10^{-15}$) and negative ($p < 5x10^{-5}$) pictures, but also in neutral pictures ($p < 8.3x10^{-10}$). The gender-dependent differences in free recall performance could not be explained by the gender-dependent differences in emotional appraisal. Importantly, female's memory advantage during free recall completely vanished in a recognition setting, indicating that gender-dependent differences in recall performance were not due to differences in memory storage. This idea was supported by a lack of gender-dependent, memory-related activation differences during encoding. In conclusion, female's memory advantage is only observed in a free recall-, but not a recognition setting and it does not depend on the higher emotional appraisal in women as compared to men.

Introduction (Max 500)

Sex differences are observed for a wide range of parameters in human research, including biological markers, physiological measurements, behavior, neuropsychological traits or neuropsychiatric disorders (Davis et al., 1999; Kudielka and Kirschbaum, 2005; McCarthy and Konkle, 2005; Holden, 2005; Tolin and Foa, 2006; Cahill, 2006, 2014; Andreano and Cahill, 2009; McLean and Anderson, 2009; Su et al., 2009; Miettunen and Jääskeläinen, 2010; Jazin and Cahill, 2010; Balliet et al., 2011; Bao and Swaab, 2011; Cross et al., 2011; Trent and Davies, 2012; Ingalhalikar et al., 2014). Sex is defined by the sex chromosomes as well as by gender identity, which includes psychological, behavioral, and social aspects (Egan and Perry, n.d.; Meyer-Bahlburg, 2010).

Episodic memory is a complex polygenetic behavioral trait, influenced by genetic and environmental factors and their interactions (Read et al., 2006; Volk et al., 2006; Papassotiropoulos and de Quervain, 2011). An important modulating factor for episodic memory performance is the perceived emotionality of the material (Roozendaal and McGaugh, 2011). Specifically, the more arousing information is perceived, the more likely it will be remembered (LaBar and Cabeza, 2006). This memory-enhancing effect of emotional arousal is partially mediated through an activation of the amygdala (Cahill et al., 1996; McGaugh and Roozendaal, 2002; McGaugh, 2004).

There is evidence that men and women react differently on emotional material (Gard and Kring, 2007). Especially for aversive material, it has been shown that women rate emotional stimuli as more arousing in comparison to men and additionally react stronger to aversive pictures measured by physiological responses like event-related potentials (ERPs), electromyographic (EMG), and startle response (Bradley et al., 2001; Gard and Kring, 2007; Lithari et al., 2010).

Further, there is evidence that females outperform males in episodic memory tasks related to remembering verbal material, faces and pictures (Herlitz et al., 1997, 2013; de Frias et al., 2006; Bloise and Johnson, 2007; Andreano and Cahill, 2009). This female's advantage can

already be shown in childhood and puberty (Kramer et al., 1997; Herlitz et al., 2013) and is stable over time (de Frias et al., 2006). The question arises, whether female's stronger perception of emotionally arousing information may lead to stronger encoding, thereby inducing an advantage in episodic memory performance.

Here we assessed the influence of sex on the emotional appraisal and the recollection of pictures with varying emotional content, as well as the brain activity during encoding and recognition of these pictures. The behavioral data enabled us to disentangle two questions: Firstly, whether sex differences in the perceived emotionality of pictorial stimuli are linked to differences in memory performance. Secondly, whether the female's memory advantage is based on a stronger encoding of the material. By analyzing valence-specific sex differences in the brain activity while encoding and while recognizing pictures, we aim to get hints about the neuronal underpinnings of sex-specific differences in behavior.

Material and Methods

Participants. We analysed data of N = 3'398 subjects from four different samples (see Table 1). Overall, 65% of the subjects were female and the mean age was 22.3 years (age-range 18-38). Subjects were free of any neurological or psychiatric illness, and did not take any medication at the time of the experiment. The ethics committee of the Canton Basel and Zurich approved the experiments. Written informed consent was obtained from all subjects prior to participation.

Behavioural tasks descriptions. The subjects performed on three different tasks we included in the analyses, a picture encoding task (N = 3'218 subjects) and two retrieval tasks, a free recall task (N_{max} = 3'232 subjects) and a recognition task (N = 1'220 subjects). Table 1 gives an overview of the analysed tasks and number of subjects per sample who performed the task. The picture encoding task consisted of the presentation of N_{max} = 24 pictures per valence group (negative, neutral and positive, picture set description see below). Subjects rated the presented pictures according to valence (negative – neutral – positive) and arousal (low – middle – high) on a nine-point or three-point scale. The behavioural data for the ratings corresponds to the averaged (valence- or arousal) rating per valence group. Subjects of the samples 2-4 additionally encoded 24 scrambled pictures with a geometrical object in the foreground. The object had to be rated regarding its form (vertical, symmetric, horizontal) and size (small, medium, large). In the unannounced free recall picture memory task, subjects had to freely recall these pictures after 10 min (short delay, SD) or 20-24 hours (long delay, LD). In the picture recognition task, subjects were presented 144 IAPS pictures, 72 previously seen pictures and 72 completely new pictures (24 negative, 24 neutral and 24 positive pictures). The subjects rated the pictures as either remembered, familiar or new. We used the false-alarm corrected correctly remembered values as recognition performance measurement.

Statistical analyses of the behavioural data. The rating scales (three or nine-point scale) as well as the number of stimuli (3 x 10 or 3 x 24) differed between samples. Therefore, it was necessary for the overall analyses to *z*-transform the data. To standardize the output of the different analyses, we *z*-transformed all task performances for each sample separately. Hence, we could not test for differences between samples (main effect sample).

Ratings (valence and arousal) and the memory performances (short-delay free recall, long-delay free recall, recognition) were analysed by calculating five main (mixed) models with subject as random effect, and sex (female, male), valence group (negative, positive and neutral) and the interaction term between sex and valence group as contrasts of interest (fixed effects). The models were estimated by REML (restricted maximum-likelihood estimation). Age was included as covariate in all models. Statistical tests for significance were done with *F*-tests. *Post-hoc* tests for the three different valence groups were done separately with linear models (*t*-test), with sex difference as the variable of interest.

The following additional analyses were done to investigate the free recall memory performances more in depth: 1) Short- and long-delay free recall performances were compared by calculating an overall model with time-point as an additional fixed-effect and the three-way interaction between sex x valence x time-point. 2) To correct for the impact of ratings on memory performance, we additionally included the subjective valence and arousal ratings as possible predictive variables of the memory performance in the mixed models. These models were labelled as "full models". The main models including age, sex and memory performance were labelled as "reduced models". Estimation was done for these analyses with Maximum-Likelihood. Full and reduced models were compared with the log-likelihood test.

In the case of group comparisons (males vs. females) we estimated Cohens´ *d* as effect size measurement. The estimate of *d* was based on the *t*-value of the linear models, but not on the mean and standard deviation of the task performance. Therefore, *d* is corrected for the effect of all confounding variables included in the linear model. By convention, $d = 0.2$ is considered to be a small effect, $d = 0.5$ to be an intermediate effect and $d = 0.8$ to be a large effect (Cohen, 1992). Due to the factor coding in our analyses, a positive *d* means that females scored higher on

a given phenotype in comparison to males. Effect sizes were not computed for repeated measurements, as these effect size calculations are influenced by the correlation between the repeated measurements.

All calculations were done in R (R Core Team, 2012), the mixed model calculations were done with the nlme-package (Pinheiro et al., 2012). All models were calculated with full datasets per subject, which results in an orthogonal design regarding repeated measurements. All reported *p*-values were nominal *p*-values. To account for the fact that we calculated five main models for the five phenotypes (valence rating, arousal rating, short-delay free recall, long-delay free recall and recognition), only results with a *p*-value < 0.01 will be called statistically significant. *p*-values smaller than 1×10^{-16} were not expressed with exact numbers.

Study description sample 1: The experiment took place on two consecutive days in lecture halls in groups of approx. 30 subjects. In the following, we describe the parts of the experiment that were relevant for our analyses. On day 1, subjects received information about the study and written informed consent was obtained. Approx. 40 minutes later the picture-related tasks began: Participants were presented the pictures (3 x 10, set 1 see below) from the picture encoding task and had to rate every picture after its presentation according to valence and arousal on a nine-point scale (duration: 5 minutes). After a distraction task (decision-making task) lasting 10 min subjects had to freely recall the pictures with a time limit of 6 minutes. On the second day, approx. 8 min after arrival, subjects were asked to freely recall the pictures from day one (24 h delayed recall), again with a time limit of 6 minutes. The total length of the experimental procedure on day 1 was approx. 2.5 hours, and on day 2 approx. 50 min. Participants received 70.- CHF for their participation.

Study description sample 2: The experiment took place on three days in groups of 1-7 subjects. Here we describe the parts of the experiment at day 2 and 3 (two consecutive days) that were relevant for our analyses. On day 2 after approx. 1.5 h the picture-related tasks began: Participants received instructions and were trained on the picture encoding task and a working memory task (N-back). After training, participants performed on the picture encoding task (20 minutes, 3 x 24 meaningful pictures, set 2 see below, 1 x 24 scrambled pictures). While encoding

the pictures, subjects had to rate the perceived valence and arousal of each picture on three-point scales. The working memory task (10 minutes) served as a distraction task. This was followed by the unannounced free recall test (no time limit) of the pictures. On day 3 after approx. 15 min the second picture-task related block took place: Participants completed again the picture encoding task (20 minutes) with a new set of emotional and neutral pictures (3 x 24 pictures). Again they rated the perceived valence and arousal of each picture on 3-point scales. Afterwards they performed the working memory task (10 minutes). Participants were then asked to freely recall (no time limit) the pictures seen 10 minutes earlier and in addition the pictures from day 2 (20 h delayed recall). The total length of the experimental procedure on day 2 was approx. four hours, and on day 3 two hours. Participants received 25.- CHF/h for participation. This is an ongoing study.

Study description sample 3 & 4: Study design and procedures were mostly identical between sample 3 & 4, which were conducted in two different sites on two different MRI scanners. The study of sample 3 was the pre-study of sample 4 with slight differences in scanner procedures. After receiving general information about the study and giving their written informed consent, participants were instructed and then trained on the picture task and a working memory (N-back) task they later performed in the MR-scanner. After training, participants were positioned in the scanner. Subjects received earplugs and headphones to reduce scanner noise. Their head was fixed in the coil using small cushions and they were instructed not to move their heads. Pictures were presented in the scanner using MR-compatible LCD goggles (VisualSystem, NordicNeuroLab, Bergen, Norway). Eye correction was used when necessary. Functional MR-images were acquired during the encoding of the pictures task (3 x 24 meaningful pictures, set 2 see below, 1 x 24 scrambled pictures) and during the working memory task. Participants spend 30 minutes in the scanner (20 minutes picture encoding task, 10 minutes working memory task). After the presentation of each picture, subjects had to rate the perceived valence and arousal on a three-point scale. The working memory task served as distraction task. After completing the tasks, participants left the scanner for the unannounced free recall test of the pictures. After finishing the free recall subjects were instructed and trained

on the recognition task outside the scanner. Following training subjects were again positioned in the MR-scanner. In the next 20 minutes they solved the recognition task (old picture in combination with new pictures from set 3 as described below) and in the last 20 minutes structural scans were acquired. The total length of the experiment procedure was approx. 3 to 4.5 hours. Participants received 25.- CHF/h for participation. The study of sample 4 is an ongoing study.

Description of the used pictures sets. On the basis of normative valence scores pictures from the International Affective Picture System (IAPS; Lang, Öhman, & Vaitl, 1988) were assigned to emotionally negative, neutral and positive picture groups (ranges for each set separately per valence; set 1: negative: 1.5-3.7, neutral: 4.6-5.5, positive: 5.6-8.2; set 2: negative: 1.4-3.5, neutral: 4.4-5.6, positive: 7.1-8.3; set 3: negative: 1.8-3.6, neutral: 4.5-5.7, positive: 7.0-8.3). For sets 2 an 3 neutral pictures (set 2: 8 pictures, set 3: 6 pictures) from in-house standardized pictures sets were selected in order to equate the pictures sets for visual complexity and content (e.g. human presence).

(f)MRI data acquisition (sample 4 only). Measurements were performed on a Siemens Magnetom Verio 3 T wholebody MR unit equipped with a twelve-channel head coil. Functional time series were acquired with a single-shot echo-planar sequence using parallel imaging (GRAPPA). We used the following acquisition parameters: TE (echo time) = 35 ms, FOV (field of view) = 22 cm, acquisition matrix = 80 × 80, interpolated to 128 × 128, voxel size: 2.75 × 2.75 × 4 mm^3, GRAPPA acceleration factor R = 2.0. Using a midsaggital scout image, 32 contiguous axial slices placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a TR (repetition time) = 3000 ms ($\alpha = 82°$) were acquired using an ascending interleaved sequence. A high-resolution T1-weighted anatomical image was acquired using a magnetization prepared gradient echo sequence (MPRAGE, TR=2000 ms; TE=3.37 ms; TI=1000 ms; flip angle=8; 176 slices; FOV=256 mm).

MRI construction of a population-average anatomical probabilistic atlas. Automatic segmentation of the subjects' T1-weighted images was used to build a population-average probabilistic anatomical atlas. More precisely, each participant's T1-weighted image was first

automatically segmented into cortical and subcortical structures using FreeSurfer (version 4.5, http://surfer.nmr.mgh.harvard.edu/, Fischl et al., 2002). Labelling of the cortical gyri was based on the Desikan-Killiany Atlas (Desikan et al., 2006), yielding 35 regions per hemisphere. The segmented T1 image was then normalized to the study-specific anatomical template space using the subject's previously computed warp field, and affine-registered to the MNI space. Nearest-neighbour interpolation was applied, in order to preserve labelling of the different structures. The normalized segmentations were finally averaged across subjects, in order to create a population-average probabilistic atlas. Each voxel of the template could consequently be assigned a probability of belonging to a given anatomical structure, based on the individual information from the $N = 612$ subjects.

Experimental design fMRI picture encoding task. We used an event-related design consisting of 100 trials, including 2 primacy and 2 recency trials depicting neutral information, 24 scrambled pictures, and 24 pictures per valence category (positive, negative, neutral). The pictures were presented for 2.5 seconds in a quasi-randomized order so that at maximum four pictures of the same category occurred consecutively. A fixation-cross appeared on the screen for 500 ms before each picture presentation. Trials were separated by a variable inter-trial period (period between appearance of a picture and the next fixation cross) of 9-12 seconds (jitter). During the inter-trial period, participants subjectively rated the picture showing scenes according to valence (positive, neutral, negative) and arousal (high, medium, low) on a three-point scale (Self Assessment Manikin, SAM) by pressing the button with the finger of their dominant (right-hander: 97%; left-hander: 72%) or non-dominant hand. For scrambled pictures, participants rated form (vertical, symmetric, horizontal) and size (small, medium, large) of the geometrical object in the foreground.

Experimental design fMRI picture recognition task. We used an event-related design consisting of 144 trials. Per trial a pictures from two different sets was presented. Each set contained 72 pictures (24 pictures for each stimulus category). The two sets of stimuli were either new (i.e. not presented before) or old (i.e. presented during the picture encoding task). The pictures were presented for 1 second in a quasi-randomized order so that at maximum four

pictures of the same category (i.e. negative new, negative old, neutral new, neutral old, positive new, positive old) occurred consecutively. A fixation-cross appeared on the screen for 500 ms before each picture presentation. Trials were separated by a variable inter-trial period of 6–12s (jitter) that was equally distributed for each stimulus category. During the inter-trial period, participants subjectively rated the picture as remembered, familiar or new on a three-point scale by pressing a button with the finger of their dominant (right-hander: 97%; left-hander: 72%) or non-dominant hand.

fMRI analyses - applied software. Pre-processing and first level analyses were performed using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK; http:// www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab R2011b (The Mathworks Inc., Natick, MA, USA). Second level analyses were done by using GLM Flex (Martinos Center & Mass General Hospital, Charlestown, MA, USA; http://nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz /Aarons_Scripts.html) in Matlab. GLM Flex is capable of dealing with missing values. The region-of-interest (ROI) analyses were done in R (R Core Team, 2012), the mixed model calculations were done with the nlme-package (Pinheiro et al., 2012).

fMRI pre-processing. Volumes were slice-time corrected to the first slice and realigned using the 'register to mean' option. A mean image was generated from the realigned series and coregistered to the structural image. The functional images and the structural images were spatially normalized by applying DARTEL, which leads to an improved registration between subjects. Normalization incorporated the following steps: 1) Structural images of each subject were segmented using the “New Segment” procedure in SPM8. 2) The resulting gray and white matter images were used to derive a study-specific group template. The template was computed from a subpopulation of $N = 612$ subjects out of this study (see above: Construction of a population-average anatomical probabilistic atlas). 3) An affine transformation was applied to map the group template to MNI (Montreal Neurological Institute) space. 4) Subject-to-template and template-to-MNI transformations were combined to map the functional images to MNI

space. The functional images were smoothed with an isotropic 8 mm full width at half maximum (FWHM) Gaussian filter.

fMRI first-level analyses and parameter estimation. Intrinsic autocorrelations were accounted for by AR(1) and low-frequency drifts were removed via high-pass filter (time constant 128 s). For each subject, evoked hemodynamic responses to event-types were modelled with a delta function corresponding to presentation of each stimulus category convolved with a canonical hemodynamic response function within the context of a general linear model (GLM). Button presses and rating scale presentation during the ratings were modelled separately. In addition, six movement parameters from spatial realigning were included as regressors of no interest. Pictures accounting for possible primacy and recency effects were excluded from statistical analysis.

All models were built separately for the three valence categories positive, neutral and negative. Activity during the encoding of pictures was assessed in three different ways: (I) By contrasting activity during the presentation of meaningful pictures against activity during the presentation of scrambled stimuli. (II) By contrasting activity during the presentation of later remembered pictures against activity during the non-remembered pictures. (III) By investigating a linear valence- and arousal-dependent modulation of signal intensity using parametric analysis (Büchel, Holmes, Rees, & Friston, 1998). The parametric analyses were based on the subject-specific ratings per picture. Therefore, we had to exclude all subjects with monomorphic ratings within one valence group (Number of excluded subject per valence group for valence rating: positive $N = 14$, negative $N = 52$, neutral $N = 18$; Number of excluded subject per valence group for arousal rating: positive $N = 3$, negative $N = 2$, neutral $N = 29$). The activity during the recognition of pictures was assessed by contrasting activity during the presentation of old pictures against activity during the presentation of new pictures (IV).

fMRI group analyses. The parameters estimated for each subject separately in the first-level analysis were then entered in the second-level (group) analysis as dependent variables. The minimum number of subjects per voxel was set to be 150. The maximum number of subjects for analyses I, II and III (encoding) was $N_{max} = 696$, and for recognition (IV) $N = 686$. For three

analyses, i.e. (I) encoding of meaningful vs. scrambled pictures, (II) encoding of remembered vs. non-remembered pictures and (IV) recognition of old vs. new pictures, we calculated an ANOVA with sex as between-factor (male, female), valence as within-factor (positive, neutral, negative) and the interaction term between sex and valence. Statistical tests of significance were done using *F*- and *t*-tests. The minimum cluster size was set to 5 voxel and we applied a family-wise error (FWE) correction for the significance threshold on whole-brain (WB) level of $P_{FWE\text{-}WB} < 0.05$: Meaningful vs. scrambled: $F_{(2,2082)} \geq 12.77$, $t_{(2082)} \geq/\leq \pm 4.49$; Remembered vs. non-remembered: $F_{(2,2082)} \geq 12.80$, $t_{(2082)} \geq/\leq \pm 4.49$. Old vs. new: $F_{(2,2052)} \geq 13.03$, $t_{(2052)} \geq/\leq \pm 4.54$.

Due to the relevance of the medial temporal lobe (hippocampus, parahippocampal gyrus and entorhinal cortex) and amygdala for (emotional) memory performance (Cabeza & Nyberg, 2000; de Quervain et al., 2003; Henke et al., 1999; Milner, 1972; Phelps, 2004; Schacter & Wagner, 1999) we performed *post-hoc* additional small-volume corrected (SVC) analyses in the same way as done on WB level. By focusing on these regions we lowered the significant threshold to $P_{FWE\text{-}SVC} < 0.05$: Meaningful vs. scrambled: $F_{(2,2082)} \geq 8.78$, $t_{(2082)} \geq/\leq \pm 3.56$; Remembered vs non-remembered: $F_{(2,2082)} \geq 8.80$, $t_{(2082)} \geq/\leq \pm 3.57$. Old vs. new: $F_{(2,2052)} \geq 8.95$, $t_{(2052)} \geq/\leq \pm 3.60$.

Additionally, we identified brain regions associated with the subjective valence or arousal ratings (analysis III, linear relationship). Statistical tests of significance were done using *t*-tests. Minimum cluster size was set to 5 voxel, the FWE correction on WB level to $P_{FWE\text{-}WB} < 0.05$: arousal: positive pictures $t_{(692)} \geq/\leq \pm 4.64$, negative pictures $t_{(693)} \geq/\leq \pm 4.66$, neutral pictures $t_{(666)} \geq/\leq \pm 4.70$; valence: positive pictures $t_{(681)} \geq/\leq \pm 4.63$, negative pictures $t_{(643)} \geq/\leq \pm 4.68$, neutral pictures $t_{(677)} \geq/\leq \pm 4.61$.

fMRI region of interest (ROI) analysis. From those voxel clusters showing a significant interaction effect between sex and valence at the group-level we extracted the subject-specific parameters estimated in the first-level analysis. Next, we averaged the parameter estimates within each valence group and cluster for each subject (averaged first-level estimates per subject, valence and ROI). All further analyses were done using linear (mixed) models in combination with ANOVA. The (averaged first-level) parameter estimates were again assigned

as dependent variable. In case of mixed models estimation was done by REML. Statistical tests of significance were done using *F*- and *t*-tests. Age was included as covariate in all models. Subjects were treated as random effect. Per ROI we calculated two analyses:

The first analysis was performed to confirm and extent the results of the fMRI second-level ANOVA. Therefore, we included sex and valence and the interaction term between sex and valence as fixed effects. We performed *post-hoc* tests to clarify the source of interaction, contrasting two of the three possible valence groups against each other (negative vs. neutral, negative vs. positive, positive vs. neutral).

The next steps were done to filter all the most relevant regions regarding specificity of effects for the negative picture category. We started filtering out all regions without a significant main effect of sex for the negative picture category. The following analyses were performed to investigate the linear relationship between the first-level parameter estimates and the task performances (behavioural data) especially of the negative and neutral group. Task performances were the averaged ratings and memory performances (summary statistics approach regarding the performances). In these models task performance, sex and valence group were assigned as fixed effects. To look for negative-specific effects, we also calculated an interaction between task performance and valence group for the negative and neutral valence groups only. All reported *p*-values were nominal *p*-values. The significance threshold was adapted to $p < 0.002$ to account for the number of extracted ROIs (encoding meaningful vs. scrambled 25 ROIs).

Results

Task 1: Picture encoding task - valence and arousal ratings

Behavioural data

Across both sexes, subjects' averaged valence and arousal ratings showed substantial differences between valence groups (main effect valence, valence rating: $F_{(2,6432)} = 50731.97$, $p < 1 \times 10^{-16}$; main effect valence, arousal rating: $F_{(2,6432)} = 12763.61$, $p < 1 \times 10^{-16}$). *Post-hoc* tests showed, that the pictures from the emotional valence groups were significantly more extremely rated compared to the neutral pictures (valence rating positive vs. neutral: $t_{(3217)} = -149.13$, $p < 1 \times 10^{-16}$, negative vs. neutral: $t_{(3217)} = -190.12$, $p < 1 \times 10^{-16}$; arousal rating positive vs. neutral: $t_{(3217)} = -93.27$, $p < 1 \times 10^{-16}$, negative vs. neutral: $t_{(3217)} = 65.67$, $p < 1 \times 10^{-16}$; see figure 1 A and B).

There were significant interaction effects between sex and valence group on the valence rating ($F_{(2,6432)} = 95.5$, $p < 1x10^{-16}$) and on the arousal rating ($F_{(2,6432)} = 74.93$, $p < 1x10^{-16}$; see figure 1). *Post-hoc* tests showed that females rated the valence and the arousal especially of negative emotional material more extreme than males, with medium effect sizes (valence: $t_{(3215)} = -13.84$, $p < 1x10^{-16}$, $d = -0.51$; arousal: $t_{(3215)} = 12.58$, $p < 1x10^{-16}$, $d = 0.47$). The ratings of positive material were also significantly more extreme in females (valence: $t_{(3215)} = 4.09$, $p = 4.3 \times 10^{-5}$, $d = 0.15$; arousal: $t_{(3215)} = 3.73$, $p = 2 \times 10^{-4}$, $d = 0.14$), but with small effect sizes. There were no significant differences between the two sexes for the ratings of neutral stimuli (valence: $t_{(3215)} = -1.5$, $p = 0.13$, $d = -0.06$; arousal: $t_{(3215)} = 1.55$, $p = 0.12$, $d = 0.06$).

fMRI data

Since we observed sex-specific differences in emotional ratings of negative and positive, but not neutral pictures, we were interested if we can identify a neuronal correlate explaining these (short-term) differences in rating. In the first-level analysis, activity during the encoding of pictures was assessed by contrasting activity during the presentation of meaningful pictures against activity during the presentation of scrambled stimuli (positive vs. scrambled, neutral vs.

scrambled, negative vs. scrambled). In the (second-level) group analysis, we calculated an ANOVA with sex as between-factor (male, female), valence as within-factor (positive, neutral, negative) and the interaction term between sex and valence. In the behaviour, we observed a sex x valence interaction effect regarding valence and arousal ratings. Therefore, our main interest was also on the sex x valence interaction effects in the fMRI analyses. We identified significant ($p_{FWE\text{-}WB} < 0.05$) cluster for the interaction effect between sex and valence in several regions with a pronunciation on motor-relevant regions frontal, parietal and in the cerebellum (see Table 2 and Figure 2). No additional suprathreshold clusters were identified when applying SVC ($p_{FWE\text{-}SVC} < 0.05$) for bilateral medial temporal lobe regions (hippocampus, parahippocampal gyrus, entorhinal cortex, and amygdala) only. For the results of the main effects sex and valence see Figure 3.

In the ROI analysis we firstly identified for all clusters the origin of the significant interaction between sex and valence. These *post-hoc* tests showed that in all but two regions, the precentral gyrus and the lingual gyrus (see Table 2), the negative valence group drove the significant sex x valence effect, meaning that the differences between negative and positive as well as negative and neutral pictures became significant, but not the difference between positive and neutral pictures.

In the next step we filtered out all regions, which additionally show a significant main effect of sex for negative pictures only. In all cases females showed a higher activation than males within the negative valence group (see Table 2). Next, we filtered out all regions which show A) a significant correlation with the averaged subject's valence- or arousal rating of the negative pictures only, and eventually B) an additional significant interaction between the subject's averaged valence or arousal rating and the neutral and negative valence groups. The overall picture indicates, that by applying these additional filters, we identified motor-relevant regions (see Table 2 regions marked with a star), which were specifically associated with the valence- and arousal ratings of negative pictures and were more active in females in comparison to males. Figure 4 shows exemplarily the results for the filtering steps within one ROI, which

survives all steps for the valence (A) and arousal (B) rating. By applying the same filter steps for the short delay memory performance none of these regions survives the filtering.

To visually confirm these results, we investigated, separately for each valence group, the linear relationship between fMRI signal intensity and ratings using parametric modulation in the first level analyses. We superimposed the sex x valence ROIs on the activation maps of valence and arousal ratings for the negative, neutral and positive valence group. By combining these two activation maps, it was possible to visualize that sex x valence ROIs were preferentially located in regions, which were correlated especially with the ratings of the negative valence group (see Figure 2).

To summarize, the behavioural results showed that women rated especially negative pictures as more arousing and negative than men. The fMRI interaction analysis for sex and valence comparing meaningful vs. scrambled pictures identified regions, which were specifically stronger activated in females in comparison to males when viewing negative pictures only. Additionally, these regions were associated with the ratings of the negative pictures and can be grouped as mainly motor-relevant regions and the posterior cingulate.

Task 2: Picture memory task – delayed recall

Overview

Emotionally arousing information is generally better remembered than neutral information. Therefore the question arises, whether the stronger ratings of females are associated with differences in memory performance, favouring females in case of emotional information.

Behavioural data

Across both sexes, subjects' memory performances showed substantial differences between valence groups (main effect valence SD: $F_{(2,6460)} = 3742.64$, $p < 1 \times 10^{-16}$; LD: $F_{(2,3952)} = 1293.95$, $p < 1 \times 10^{-16}$). *Post-hoc* tests showed, that pictures from the positive valence group (SD: $t_{(3231)} = -79.71$, $p < 1 \times 10^{-16}$; LD: $t_{(1977)} = -48.03$, $p < 1 \times 10^{-16}$) as well as from the negative

valence group (SD: $t_{(3231)} = 68.34$, $p < 1 \times 10^{-16}$; LD: $t_{(1977)} = 39.13$, $p < 1 \times 10^{-16}$; see figure 1 C and D) were significantly better remembered than neutral pictures.

There was a significant interaction effect between sex and valence group on the short delay (10 min delayed) free recall of the pictures ($F_{(2,6460)} = 35.47$, $p = 4.4 \times 10^{-16}$). *Post-hoc* tests showed, that although females overall performed better than males, this advantage was most pronounced for positive material (positive: $t_{(3229)} = 12.15$, $p < 1 \times 10^{-16}$, $d = 0.45$; neutral: $t_{(3229)} = 6.16$, $p = 8.3 \times 10^{-10}$, $d = 0.23$; negative: $t_{(3229)} = 4.06$, $p = 5 \times 10^{-5}$, $d = 0.15$). The specific advantage of remembering positive material for females could also be seen in the long delay (20-24 h delayed) free recall task (sex x valence: $F_{(2,3952)} = 21.75$, $p = 4 \times 10^{-10}$; main effect sex positive: $t_{(1975)} = 10.44$, $p < 1 \times 10^{-16}$, $d = 0.5$; neutral: $t_{(1975)} = 5.58$, $p = 2.8 \times 10^{-8}$, $d = 0.27$; negative: $t_{(1975)} = 5.1$, $p = 3.6 \times 10^{-7}$, $d = 0.25$). The effect size for female's advantage of positive material was medium. There was no significant three-way interaction ($F_{(2,9880)} = 0.36$, $p = .70$) between valence, sex and time-point (short- versus long-delayed recall). Therefore, the women's special advantage for positive pictures did not change over the two time points. This result in comparison to the result of the ratings showed a different profile. Women showed a stronger appraisal especially of the negative pictures but a better memory performance especially for the positive pictures. Therefore, these two effects are most likely not connected to each other. Furthermore, females showed a better memory performance for neutral pictures, although there was no difference in emotional appraisal for this category.

To confirm the result that the above described sex-specific memory effects were independent of the influence of the ratings of the subject, we expanded our (reduced) linear model. We included the averaged valence and arousal ratings as well as their interaction terms with valence group in our linear model (full model). We tested overall, whether these additional variables explained a significant amount of variance of the subject's memory performance, and whether the effect-sizes of the female's advantage in memory performance changed when taking the additional variables into account: A) For the short delayed memory performance ($N = 3212$) the additional variables added significant information to the model (full vs. reduced model LR = 118.93, $p < 1 \times 10^{-16}$). The interaction term between sex and valence of the full model was

significant ($F_{(2,6414)}$ = 34.55, p = 1.1 x 10^{-15}). The effect sizes of the sex-effect for the three valence groups were comparable between the full model (positive: d = 0.44; neutral: d = 0.24; negative: d = 0.12) and the reduced model (positive: d = 0.45; neutral: d = 0.23; negative: d = 0.15). B) For the long delayed memory performance (N = 1971) the additional variables also added significant information to the model (full vs. reduced model LR = 27.38, p = 1.2 x 10^{-4}). The interaction term between sex and valence of the full model was significant ($F_{(2,3932)}$ = 20.27, p = 1.7 x 10^{-9}). The effect size for the positive pictures was comparable for the full model (positive: d = 0.50; neutral: d = 0.28; negative: d = 0.23) and the reduced model (positive: d = 0.51; neutral: d = 0.28; negative: d = 0.25).

Taken together, compared to males, females rated especially negative pictures as more arousing and more negative during the presentation and displayed stronger brain activation in mainly motor-relevant regions. However, in the free-recall test, females outperformed males not only in positive and negative pictures, but also in neutral pictures. These data suggest that the gender-dependent differences in free recall were independent from gender-dependent differences in emotional appraisal.

fMRI data

From the previous fMRI analysis during encoding, contrasting meaningful vs. scrambled pictures, we did not find an involvement in MTL regarding the sex x valence interaction effect. Thus, there was no hint for a special recruitment of MTL regions for emotional pictures that could explain the women's advantage in memory performance. To further investigate this issue, we added another fMRI analysis during encoding contrasting remembered vs. not remembered pictures (first level analysis: positive, negative and neutral remembered vs. not remembered, subsequent memory effect). We calculated an ANOVA (second level analysis) with sex as between-factor (male, female), valence as within-factor (positive, neutral, negative) and the interaction term between sex and valence. We observed a sex x valence interaction effect regarding memory performance in the behavioural data, with females showing especially for positive pictures a better memory performance. Therefore, our main interest was also on the sex

x valence interaction effects in the fMRI analyses, which showed no significant result. Also the SVC, which restricted the analysis to the MTL, did not show any significant clusters for the interaction term. For the main effect of sex no suprathreshold cluster was found. For the results of the main effect of valence see Figure 4.

To summarize, females showed a memory performance advantage mainly for positive pictures, which was independent of their more extreme ratings in the encoding phase of the experiment. The fMRI interaction analysis for sex and valence comparing remembered vs. non-remembered pictures showed no significant cluster on whole-brain level. Even at lower threshold (SVC) we did not identify regions in the MTL, which were especially recruited by females when encoding positive pictures.

Task 3: Picture memory task – recognition

Overview

We did not find evidence for memory-relevant sex differences in the encoding phase of the memory task. Therefore, the women's advantage in the free recall setting could be due to i) a stronger memory formation after encoding or ii) more successful retrieval in the free recall setting. Differences in memory formation should lead to a setting-independent memory performance advantage, whereas retrieval differences might depend on the retrieval setting. To further elaborate these possibilities, we investigated sex differences in a recognition memory task (false alarm corrected recognition performance).

Behavioural data

Across both sexes, subjects' memory performances differed substantially between the three valence groups ($F_{(2,2436)} = 172.97$, $p < 1 \times 10^{-16}$; see figure 1 E). *Post-hoc* tests showed, that pictures from the positive ($t_{(1219)} = -4.55$, $p = 6.0 \times 10^{-6}$) as well as negative ($t_{(1219)} = 16.77$, $p < 1 \times 10^{-16}$) valence group were significantly better remembered than neutral pictures.

There was a significant interaction effect between sex and valence group ($F_{(2,2436)} = 8.34$, $p = 0.00025$). *Post-hoc* test showed a significant advantage of males for negative pictures

($t_{(1217)} = -4.03$, $p = 6 \times 10^5$, $d = -0.24$). There was neither a significant sex difference for positive pictures ($t_{(1217)} = -0.49$, $p = 0.62$, $d = -0.03$), nor for neutral pictures ($t_{(1217)} = -1.79$, $p = 0.073$, $d = -0.11$). There was also no bonferroni-corrected ($p < 0.01$) significant main effect of sex ($F_{(1,1217)} = 4.81$, $p_{nominal} = 0.028$).

The false-alarm corrected recognition performance was based on the correctly identified old pictures minus the incorrectly remembered new pictures. To test, whether the above described sex differences can be found in both or only in one of the two performance measurements, we repeated the same analysis with the correctly identified old pictures and incorrectly remembered new pictures separately. For the correctly identified old pictures, the same interaction could be shown ($F_{(2,2436)} = 8.87$, $p = 0.00015$), but not for the incorrectly remembered new pictures ($F_{(2,2436)} = 0.21$, p = 0.81).

fMRI data

In the first-level analysis, we assessed activity during the recognition of pictures by contrasting activity during the presentation of old pictures against activity during the presentation of new pictures. In second analysis, we calculated an ANOVA with sex as between-factor (male, female), valence as within-factor (positive, neutral, negative) and the interaction term between sex and valence. In the behavioural analyses, we found a sex x valence interaction effect regarding recognition performance, with males showing especially for negative pictures a better memory performance. Therefore, our main interest was also on the sex x valence interaction effects in the fMRI analyses, which showed no significant result. Also the SVC did not show any significant clusters for the interaction term. For the results of the main effects of sex and valence see Figure 4.

Taken together, the female's memory advantage in the free recall setting was not found in the recognition setting. This suggests, that the sex-dependent differences in memory performances were retrieval setting-dependent and not due to sex-dependent differences in memory storage. Furthermore, the fMRI interaction analysis for sex and valence comparing old

vs. new pictures showed no significant cluster on whole-brain level as well as applying a small volume correction for the MTL regions only.

Discussion

By analysing the behavioural data of four different samples, comprising more than 3'300 subjects, we were able to show that the women's stronger appraisal of emotional material, especially for the negative valence, is accompanied by a stronger activation of motor-relevant brain regions and the posterior cingulate. However, this stronger reactivity in the encoding phase was not linked to sex-dependent differences in memory performance later on, although we could show that across sexes emotional stimuli were remembered better than neutral stimuli. By comparing the memory data of two different tasks, a free-recall task and a recognition task, we were able to show that sex differences regarding memory performance were retrieval setting-dependent. Specifically, women outperformed men only in the free recall task but not in recognition task, suggesting that there was no sex-dependent difference in memory storage.

The finding of a higher appraisal of emotional material in females in comparison to males, in particular for the negative valence category, is interesting in the context of vulnerability to neuropsychiatric diseases (Earls, 1987; Culbertson, 1997; Weinstock, 1999; Holden, 2005). Emotional dysregulation is a common component of many neuropsychiatric diseases (Cole et al., 1994; Kring and Sloan, 2009) and women are more likely to develop major depression, anxiety disorder, and posttraumatic stress disorder (Eysenck et al., 1991; Donaldson et al., 2007; Mohlman et al., 2007; Liu et al., 2012). In our data, the stronger reactivity of females to negative material was related to higher brain activations in motor-relevant regions and the posterior cingulate. This pattern suggests that females might be better prepared to physically react on negative events than males. Other studies that used ERPs, EMG, startle response and facial expression (Kring and Gordon, 1998; Bradley et al., 2001; Gard and Kring, 2007; Lithari et al., 2010) also indicate increased motor reactions upon emotional stimuli in females as compared to males. However, our findings suggest that the differences in emotional appraisal do no influence memory processes within the first 24 hours. These sex differences might in part be due to differences in concentrations of gonadal hormones, vasopressin, and oxytocin (van Honk

and Schutter, 2007; Andreano and Cahill, 2009; Ertman et al., 2011; Meyer-Lindenberg et al., 2011; Ackermann et al., 2012; Kret and De Gelder, 2012; Uzefovsky et al., 2012) and environmental factors such as gender-stereotypic socialization and socio-moral explanation (Fischer et al., 2004; Mathieson and Banerjee, 2011).

Regarding the females' advantage in memory tasks, it has been discussed, that the memory advantage might be confounded with a females' advantage in verbal tasks, and that it is hardly possible to disentangle these two mechanisms (Andreano and Cahill, 2009). Also in our study, better verbal abilities may have contributed to females' general advantage in the free recall task. Alternatively, females might have been more motivated than men, which might also have contributed to a better memory performance. Both verbal skills and motivational aspects are likely to play a less important role in the recognition task, resulting in a disappearance of the females' memory advantage.

In general, the here reported sex effects are, as expected (Hyde and Linn, 1988; Hyde, 2005; Lindberg et al., 2010), in a small to medium effect-size range. The examined sample size was well powered for these effect-sizes. One could criticize, that by identifying only small to medium effects, we were not able to show relevant results, although they are statistically significant. Given the nature of complex cognitive traits and complex diseases, which emerge due to the combination of genetic and environmental background and also gen-environment interactions, one would not expect a single factor to explain the lion's share of variation. In the case of sex effects, we have an obvious difference in genetic background, which additionally affects hormone level and most likely interacts with environmental factors. All these factors together conjointly result in a given complex phenotype. Considering the small to medium effect sizes of each single factor, it is important to conduct well-powered studies. Small sample size has been identified as an issue undermining the reliability of findings in neuroscience (Ioannidis, 2008; Button et al., 2013). Figure 5 provides information about the necessary sample sizes to be able to replicate the here reported behavioral results.

Taken together, the present findings suggest that the sex differences in emotional appraisal and the sex differences in free recall of pictures are two independent phenomena. The female's stronger reaction to negative stimuli is paralleled by a stronger activation of motor-relevant brain regions, but is not paralleled by a better recall of the material later on. By comparing two different memory tasks it was possible to show, that the sex differences in memory performance were retrieval setting-dependent and not due to differential memory storage. The women's advantage in free recall might result from other factors, such as motivation or verbal skills. Due to the large sample size analyzed here, we were able to reliably identify task- and valence-specific behavioral differences with small to medium effect sizes.

References

Ackermann S, Spalek K, Rasch B, Gschwind L, Coynel D, Fastenrath M, Papassotiropoulos A, de Quervain DJ-F (2012) Testosterone levels in healthy men are related to amygdala reactivity and memory performance. Psychoneuroendocrinology.

Andreano JM, Cahill L (2009) Sex influences on the neurobiology of learning and memory. Learn Mem 16:248–266.

Balliet D, Li NP, Macfarlan SJ, Van Vugt M (2011) Sex differences in cooperation: a meta-analytic review of social dilemmas. Psychol Bull 137:881–909.

Bao A-M, Swaab DF (2011) Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. Front Neuroendocrinol 32:214–226.

Bloise SM, Johnson MK (2007) Memory for emotional and neutral information: gender and individual differences in emotional sensitivity. Memory 15:192–204.

Bradley MM, Codispoti M, Sabatinelli D, Lang PJ (2001) Emotion and motivation II: sex differences in picture processing. Emotion 1:300–319.

Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, Munafò MR (2013) Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 14:365–376.

Cahill L (2006) Why sex matters for neuroscience. Nat Rev Neurosci 7:477–484.

Cahill L (2014) Fundamental sex difference in human brain architecture. Proc Natl Acad Sci U S A 111:577–578.

Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A 93:8016–8021.

Cohen J (1992) Statistical Power Analysis. Curr Dir Psychol Sci 1:pp. 98–101.

Cole PM, Michel MK, Teti LO (1994) The development of emotion regulation and dysregulation: a clinical perspective. Monogr Soc Res Child Dev 59:73–100.

Cross CP, Copping LT, Campbell A (2011) Sex differences in impulsivity: a meta-analysis. Psychol Bull 137:97–130.

Culbertson FM (1997) Depression and gender. An international review. Am Psychol 52:25–31.

Davis MC, Matthews KA, Twamley EW (1999) Is life more difficult on Mars or Venus? A meta-analytic review of sex differences in major and minor life events. Ann Behav Med 21:83–97.

De Frias CM, Nilsson L-G, Herlitz A (2006) Sex differences in cognition are stable over a 10-year period in adulthood and old age. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 13:574–587.

Donaldson C, Lam D, Mathews A (2007) Rumination and attention in major depression. Behav Res Ther 45:2664–2678.

Earls F (1987) Sex differences in psychiatric disorders: origins and developmental influences. Psychiatr Dev 5:1–23.

Egan SK, Perry DG (n.d.) Gender identity: A multidimensional analysis with implications for psychosocial adjustment.

Ertman N, Andreano JM, Cahill L (2011) Progesterone at encoding predicts subsequent emotional memory. Learn Mem 18:759–763.

Eysenck MW, Mogg K, May J, Richards A, Mathews A (1991) Bias in interpretation of ambiguous sentences related to threat in anxiety. J Abnorm Psychol 100:144–150.

Fischer AH, Rodriguez Mosquera PM, van Vianen AEM, Manstead ASR (2004) Gender and culture differences in emotion. Emotion 4:87–94.

Gard MG, Kring AM (2007) Sex differences in the time course of emotion. Emotion 7:429–437.

Herlitz A, Nilsson LG, Bäckman L (1997) Gender differences in episodic memory. Mem Cognit 25:801–811.

Herlitz A, Reuterskiöld L, Lovén J, Thilers PP, Rehnman J (2013) Cognitive sex differences are not magnified as a function of age, sex hormones, or puberty development during early adolescence. Dev Neuropsychol 38:167–179.

Holden C (2005) Sex and the suffering brain. Science 308:1574.

Hyde JS (2005) The gender similarities hypothesis. Am Psychol 60:581–592.

Hyde JS, Linn MC (1988) Gender differences in verbal ability: A meta-analysis. Psychol Bull 104:53–69.

Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, Hakonarson H, Gur RE, Gur RC, Verma R (2014) Sex differences in the structural connectome of the human brain. Proc Natl Acad Sci U S A 111:823–828.

Ioannidis JPA (2008) Why most discovered true associations are inflated. Epidemiology 19:640–648.

Jazin E, Cahill L (2010) Sex differences in molecular neuroscience: from fruit flies to humans. Nat Rev Neurosci 11:9–17.

Kramer JH, Delis DC, Kaplan E, O'Donnell L, Prifitera A (1997) Developmental sex differences in verbal learning. Neuropsychology 11:577–584.

Kret ME, De Gelder B (2012) A review on sex differences in processing emotional signals. Neuropsychologia 50:1211–1221.

Kring AM, Gordon AH (1998) Sex differences in emotion: expression, experience, and physiology. J Pers Soc Psychol 74:686–703.

Kring AM, Sloan DM (2009) Emotion Regulation and Psychopathology: A Transdiagnostic Approach to Etiology and Treatment. New York: The Guilford Press.

Kudielka BM, Kirschbaum C (2005) Sex differences in HPA axis responses to stress: a review. Biol Psychol 69:113–132.

LaBar KS, Cabeza R (2006) Cognitive neuroscience of emotional memory. Nat Rev Neurosci 7:54–64.

Lindberg SM, Hyde JS, Petersen JL, Linn MC (2010) New trends in gender and mathematics performance: A meta-analysis. Psychol Bull 136:1123–1135.

Lithari C, Frantzidis CA, Papadelis C, Vivas AB, Klados MA, Kourtidou-Papadeli C, Pappas C, Ioannides AA, Bamidis PD (2010) Are females more responsive to emotional stimuli? A neurophysiological study across arousal and valence dimensions. Brain Topogr 23:27–40.

Liu W, Wang L, Zhao S, Ning Y, Chan RCK (2012) Anhedonia and emotional word memory in patients with depression. Psychiatry Res 200:361–367.

Mathieson K, Banerjee R (2011) Peer play, emotion understanding, and socio-moral explanation: the role of gender. Br J Dev Psychol 29:188–196.

McCarthy MM, Konkle ATM (2005) When is a sex difference not a sex difference? Front Neuroendocrinol 26:85–102.

McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27:1–28.

McGaugh JL, Roozendaal B (2002) Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 12:205–210.

McLean CP, Anderson ER (2009) Brave men and timid women? A review of the gender differences in fear and anxiety. Clin Psychol Rev 29:496–505.

Meyer-Bahlburg HFL (2010) From mental disorder to iatrogenic hypogonadism: dilemmas in conceptualizing gender identity variants as psychiatric conditions. Arch Sex Behav 39:461–476.

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci 12:524–538.

Miettunen J, Jääskeläinen E (2010) Sex differences in Wisconsin Schizotypy Scales--a meta-analysis. Schizophr Bull 36:347–358.

Mohlman J, Carmin CN, Price RB (2007) Jumping to interpretations: social anxiety disorder and the identification of emotional facial expressions. Behav Res Ther 45:591–599.

Papassotiropoulos A, de Quervain DJ-F (2011) Genetics of human episodic memory: dealing with complexity. Trends Cogn Sci 15:381–387.

Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team (2012) nlme: Linear and Nonlinear Mixed Effects Models. Available at: http://cran.r-project.org/web/packages/nlme/.

1 R Core Team (2012) R: A Language and Environment for Statistical Computing. Available at:
2 http://www.r-project.org/.

3 Read S, Pedersen NL, Gatz M, Berg S, Vuoksimaa E, Malmberg B, Johansson B, McClearn GE
4 (2006) Sex differences after all those years? Heritability of cognitive abilities in old age. J
5 Gerontol B Psychol Sci Soc Sci 61:137–143.

6 Roozendaal B, McGaugh JL (2011) Memory modulation. Behav Neurosci 125:797–824.

7 Su R, Rounds J, Armstrong PI (2009) Men and things, women and people: a meta-analysis of sex
8 differences in interests. Psychol Bull 135:859–884.

9 Tolin DF, Foa EB (2006) Sex differences in trauma and posttraumatic stress disorder: a
10 quantitative review of 25 years of research. Psychol Bull 132:959–992.

11 Trent S, Davies W (2012) The influence of sex-linked genetic mechanisms on attention and
12 impulsivity. Biol Psychol 89:1–13.

13 Uzefovsky F, Shalev I, Israel S, Knafo A, Ebstein RP (2012) Vasopressin selectively impairs
14 emotion recognition in men. Psychoneuroendocrinology 37:576–580.

15 Van Honk J, Schutter DJLG (2007) Testosterone reduces conscious detection of signals serving
16 social correction: implications for antisocial behavior. Psychol Sci 18:663–667.

17 Volk HE, McDermott KB, Roediger HL, Todd RD (2006) Genetic influences on free and cued recall
18 in long-term memory tasks. Twin Res Hum Genet 9:623–631.

19 Weinstock LS (1999) Gender differences in the presentation and management of social anxiety
20 disorder. J Clin Psychiatry 60 Suppl 9:9–13.

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Table 1: Descriptive information for the included samples and tasks. For the ongoing studies, the status of the samples is from April 2013.

	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**ALL**
Percent of females	73	66	64	60	65
Mean age	21.2	22.4	24.1	22.4	22.3
Age range	18-28	18-35	18-38	18-35	18-38
Ongoing study	No	Yes	No	Yes	-
N_{max}	511	1638	104	1145	3398
Picture encoding task	9-point scale	3-point scale	3-point scale	3-point scale	
- Valence rating *N*	503	1482	102	1131	3218
- Arousal rating *N*	503	1482	102	1131	3218
Picture memory task	3x10 pictures	3x24 pictures	3x24 pictures	3x24 pictures	
- 10 min delayed recall *N*	510	1481	104	1137	3232
- 20-24 h delayed recall *N*	501	1477	0	0	1978
- Recognition *N*	0	0	101	1119	1220
fMRI Encoding	0	0	0	696	696
fMRI Recognition	0	0	0	686	686

		Whole brain analyses results					ROI results based on the averaged estimates per cluster											
							Post hoc tests				Filtering steps							
		F_{max}	Peak Voxel MNI coordinates				Sex x Valence analyses for different valence categories				HF Sex neg		HF arousal rating neg		arousal rating x valence	HF valence rating neg		valence rating x valence
Region	H		X	Y	Z	N	neg, neu & pos: *p*	neg & neu: *p*	neg & pos: *p*	pos & neu: *p*	*p*	*d*	*p*	*r*	neg & neu: *p*	*p*	*r*	neg & neu: *p*
Frontal lobe																		
paracentral lobule*	L	19.7	-13.75	-30.25	40	49	8.9e-10*	3.4e-07*	5.2e-09*	0.86	**6.2e-08***	0.42	0.0034	0.11	6.7e-12*	**5e-04***	-0.13	0.0075
precental gyrus 1	L	18.39	-57.75	5.5	0	17	5.3e-08*	0.00011*	6.1e-09*	0.13	2e-05*	0.33	0.76	0.01	0.00033*	0.67	-0.02	0.021
precental gyrus 2*	L	14.26	-46.75	0	4	6	2.1e-07*	2.7e-05*	1.6e-07*	0.45	**5.3e-12***	0.54	**0.00055***	0.13	**4.5e-11***	**0.00026***	-0.14	0.0059
precental gyrus 3*	L	19.48	-35.75	-13.75	48	51	1.8e-08*	0.00014*	6.7e-10*	0.084	**4.6e-07***	0.39	**6.1e-06***	0.17	**3.4e-14***	0.0043	-0.11	8.1e-05*
precental gyrus 4*	L	15.73	-16.5	-11	76	10	6.9e-08*	7.8e-08*	5e-05*	0.11	**6.8e-06***	0.35	0.069	0.07	1e-06*	**0.00073***	-0.13	**0.00013***
precental gyrus 5	R	14.8	60.5	8.25	4	5	1.9e-07*	3.4e-06*	1.3e-06*	0.69	3.5e-07*	0.4	0.079	0.07	3.1e-07*	0.62	-0.02	0.046
precental gyrus 6[1]	R	15.15	46.75	-2.75	52	6	6.1e-07*	0.0024	2.9e-08*	0.032	0.0025	0.24	0.28	0.04	6.9e-06*	0.22	-0.05	0.0066
superior frontal gyrus	R	19.19	8.25	2.75	64	47	3.6e-09*	5.1e-07*	5e-08*	0.98	4.6e-06*	0.36	0.14	0.06	3e-05*	0.033	-0.08	0.0034
Parietal lobe																		
inferior parietal cortex	L	14.31	-38.5	-82.5	28	9	1.3e-07*	1.1e-06*	2.6e-06*	0.4	0.15	0.11	0.41	-0.03	0.53	0.21	-0.05	0.013
precuneus cortex	L	18.27	-8.25	-49.5	52	65	8.5e-09*	4.1e-07*	3.5e-07*	0.49	0.023	0.18	0.58	0.02	5.6e-05*	0.11	-0.06	0.0065
superior parietal cortex	L	13.86	-19.25	-46.75	68	7	3.7e-07*	1.1e-05*	1.4e-06*	0.97	0.01	0.2	0.063	0.07	1.4e-13*	0.076	-0.07	0.004
supramarginal gyrus 1	L	14.11	-63.25	-22	16	5	9.3e-07*	0.00022*	2.9e-07*	0.23	3.8e-06*	0.36	0.03	0.08	2e-10*	0.035	-0.08	0.24
supramarginal gyrus 2*	L	15.37	-52.25	-27.5	20	16	7.7e-08*	2.1e-05*	1e-08*	0.56	**4.1e-07***	0.4	**0.0017***	0.12	**4.7e-16***	**0.00081***	-0.13	0.086
supramarginal gyrus 3	L	16.84	-60.5	-35.75	32	22	6.3e-08*	1.2e-05*	3e-08*	0.53	0.00023*	0.29	0.89	0.01	0.0016*	0.027	-0.09	0.05
supramarginal gyrus 4*	R	13.92	49.5	-27.5	28	11	4e-07*	3e-05*	3e-07*	0.71	**4e-06***	0.36	**8.6e-06***	0.17	**< 1e-16***	0.2	-0.05	0.064
Occipital lobe																		
cuneus cortex*	L	14.95	-13.75	-77	20	19	1.3e-07*	0.00012*	2.5e-08*	0.19	**3.4e-10***	0.49	**1.1e-14***	0.29	**2.9e-12***	**0.00046***	-0.13	**4.4e-12***
lingual gyrus 1[1]	L	16.36	-13.75	-55	-8	25	1e-07*	0.0067	6e-09*	0.0038	2.9e-06*	0.37	6.4e-12*	0.26	1.2e-10*	0.0015*	-0.12	1.1e-11*
lingual gyrus 2	R	14.61	24.75	-49.5	4	5	5.2e-07*	0.00049*	6.1e-08*	0.12	0.33	0.07	6.1e-07*	0.19	8.3e-13*	0.0055	-0.11	1.3e-06*
Cingulate cortex																		
cingulate cortex, caudal anterior division	L	15.07	0	16.5	28	10	1e-07*	3.4e-07*	0.00012*	0.041	6.7e-09*	0.45	0.55	0.02	0.24	0.48	-0.03	0.0099

cingulate cortex, posterior division	R	15.19	11	-27.5	40	16	7.2e-08*	1e-06*	3.2e-06*	0.32	1.5e-16*	0.65	0.024	0.08	1.3e-12*	0.087	-0.06	0.13
Other																		
cerebellum cortex 1	L	21.77	-33	-57.75	-52	73	1.2e-12*	1.1e-08*	9.3e-12*	0.58	8.9e-08*	0.43	0.082	0.07	0.012	0.44	-0.03	0.00057*
cerebellum cortex 2*	R	14.92	24.75	-44	-28	11	1.8e-08*	1.7e-06*	6.7e-08*	0.91	**3.5e-05***	0.32	0.0098	0.1	0.00061*	**0.00074***	-0.13	**4.4e-06***
cerebellum white matter	R	14.63	24.75	-46.75	-48	5	2.1e-07*	1.6e-05*	1.7e-07*	0.69	0.074	0.14	0.19	0.05	0.3	0.45	-0.03	0.056
Temporal lobe																		
superior temporal gyrus[2]	L	19.23	-35.75	-2.75	-24	19	3.5e-10*	1.3e-08*	2.8e-08*	0.85	1.4e-06*	0.38	0.15	0.06	0.00071*	0.053	-0.07	0.00055*

Table 2: Encoding fMRI, contrast meaningful vs. scrambled, overview about the significant brain regions for the interaction effect between sex and valence. All but two regions (marked with [1], precental gyrus 6 and lingual gyrus 1) showed a negative specific sex x valence effect in the *post-hoc* tests. Regions marked with a star (*) additionally survived all filtering steps of the ROI-analyses, which means that additionally to the sex x valence interaction effect in these regions there is a significant main effect of sex for negative pictures and a significant correlation with valence or arousal rating of negative pictures. For all cluster except the left paracentral lobule this correlation was additionally significantly stronger for negative in comparison to the neutral picture category at least for one of the two ratings. The relevant significant p-values are bold. $p < 0.002$ is called significant. H: hemisphere; N: number of voxels. [2]: Reported is the closest gray matter area identified manually.

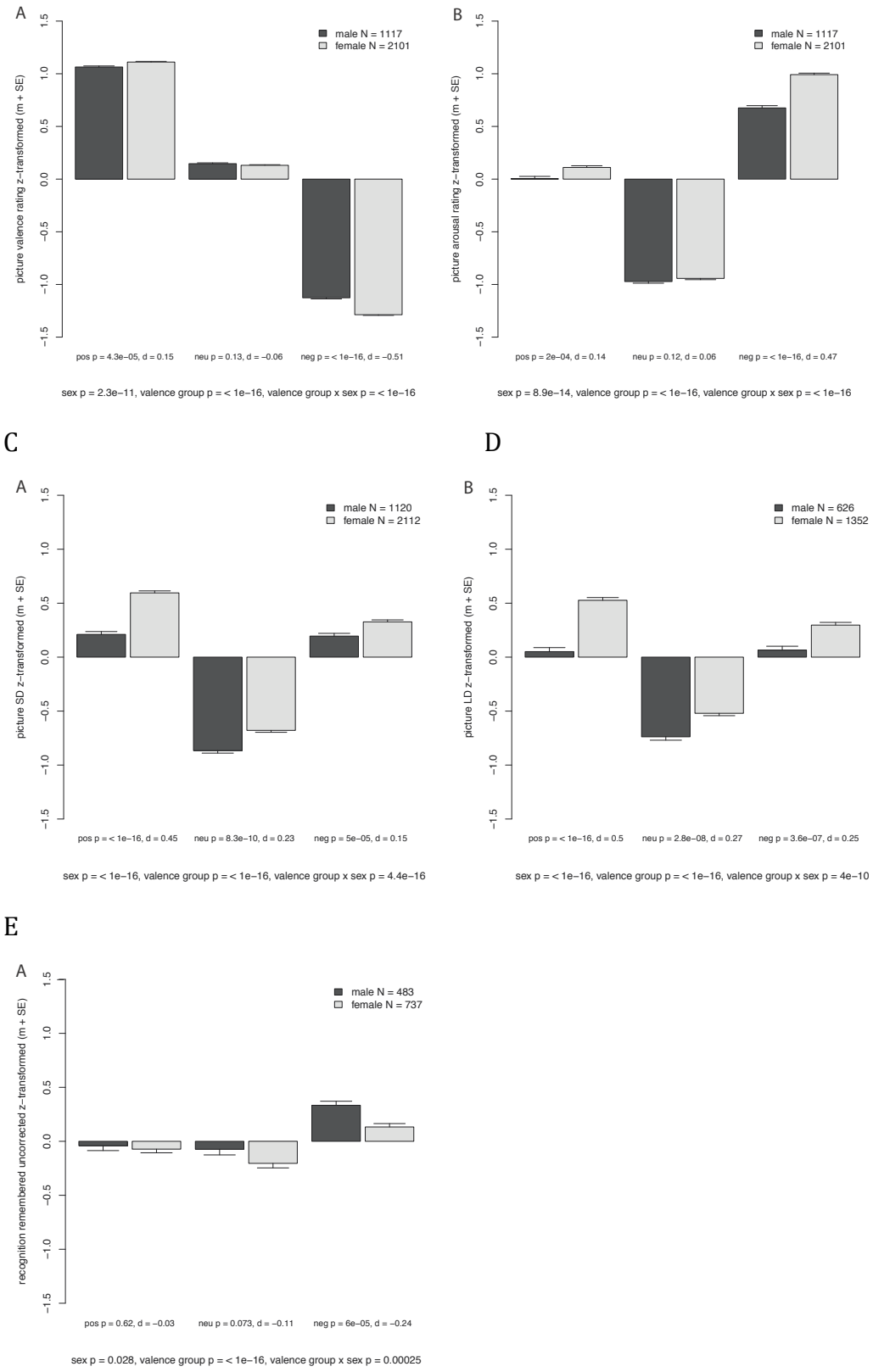

Figure 1: Results of the behavioral analyses. The task performances are *z*-transformed, therefore a negative task performance denotes, that the performance in this group was lower than the average performance. A, picture valence rating. B, picture arousal rating.

C, short delay memory performance. D, long delay memory performance. E, recognition performance. pos: positive, neu: neutral, neg: negative.

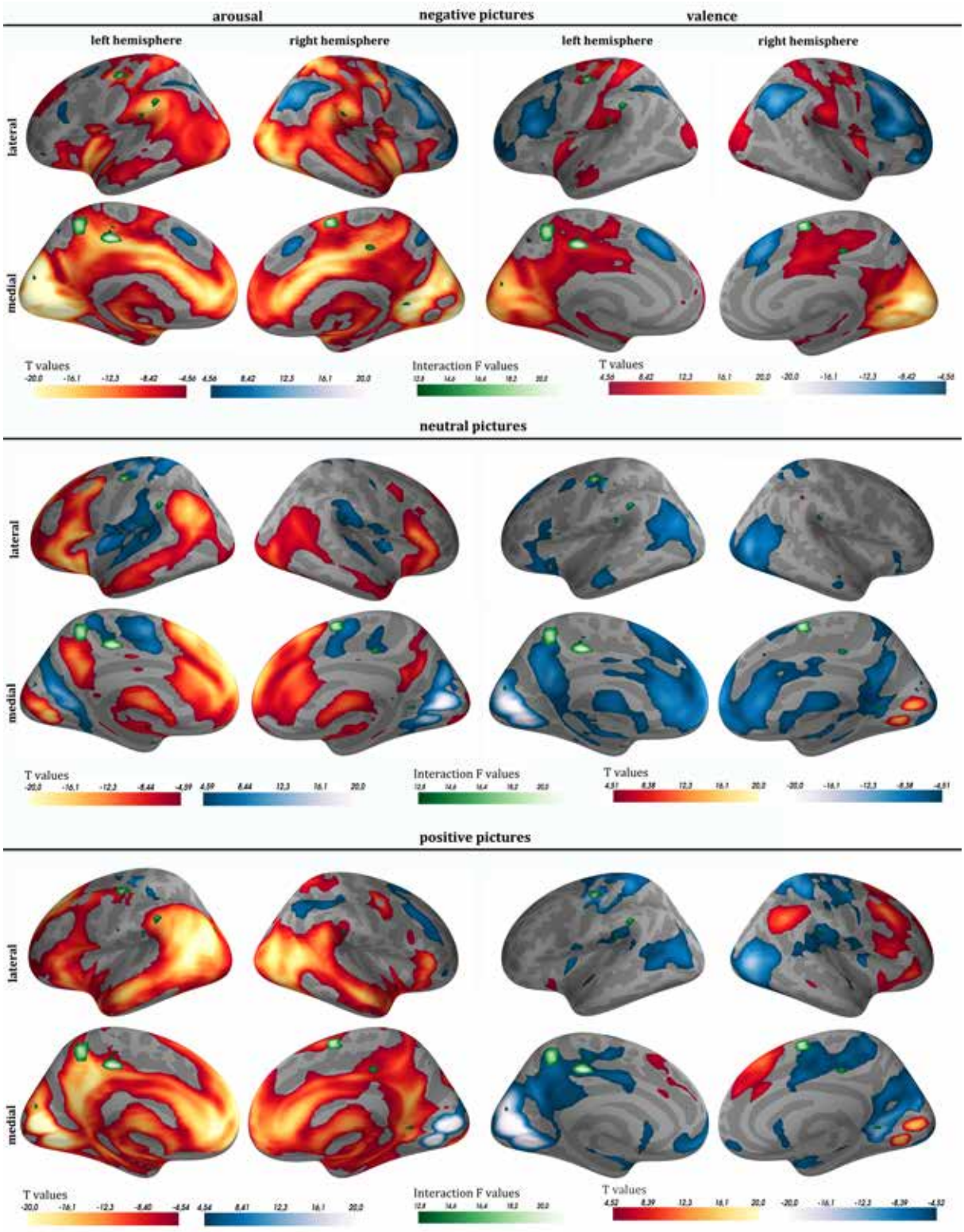

Figure 2: Visualized are the linear relationships between valence (left) and arousal (right) ratings for the picture encoding task, separately for the three valence groups (negative, neutral, positive). Red colors indicate higher arousal or more negative valence rating, whereas blue colors indicate lower arousal and more positive valence rating. Superimposed in green are the clusters, which showed a significant interaction between

sex and valence (green) in the meaningful vs. scrambled contrasts of the picture encoding task.

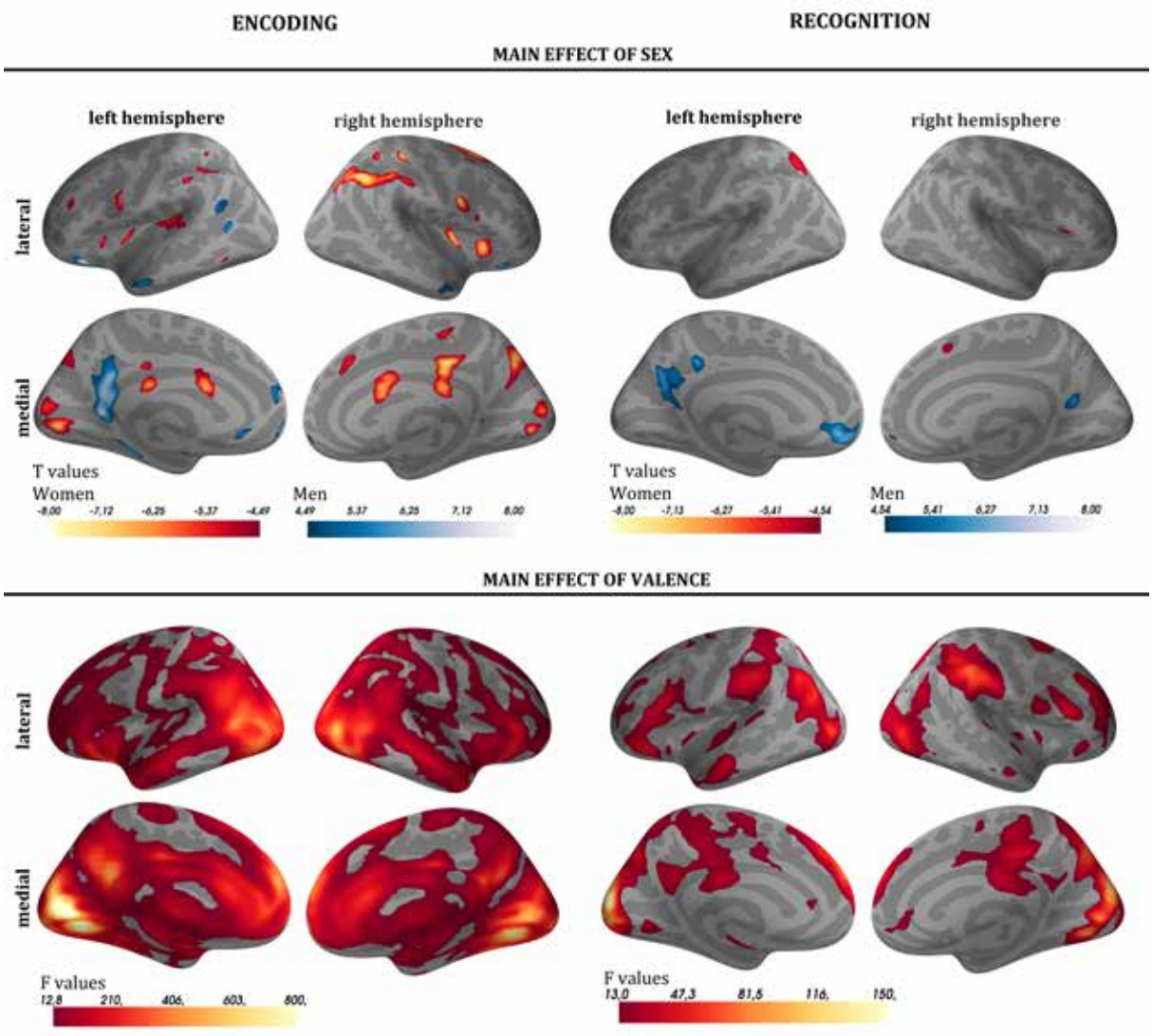

Figure 3: Main effects of sex and valence for the picture encoding task contrasting meaningful vs. scrambled pictures (left) and the recognition task contrasting remembered vs. non-remembered pictures (right). For the main effect of sex (top) red indicate that for females in comparison to males this contrast was more pronounced, whereas blue indicates that fore males in comparison to females this contrast was more pronounced. For the main effect of valence (bottom) the more yellow the regions are, the higher the differences for the contrasts were fore the three valence categories.

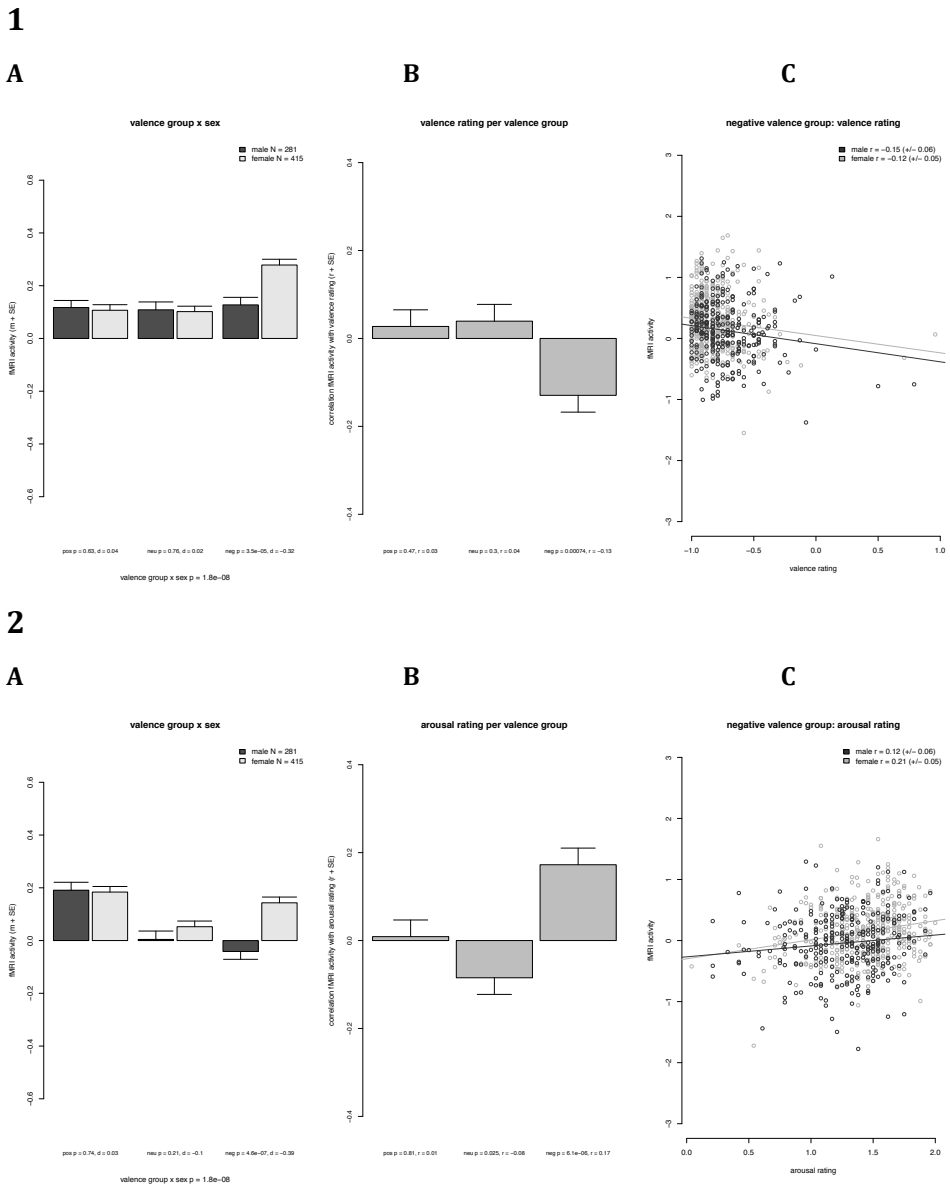

Figure 4: Picture encoding task meaningful vs. scrambled, ROI right cerebellum cortex (A, cluster number 3) and left precentral gyrus (B, cluster number 19). Depicted are the region-of-interest analyses steps. A, shows the significant interaction between sex and valence. Positive values indicate that meaningful pictures in comparison to scrambled pictures were followed by a higher brain activation of the subjects. B, shows the association between the fMRI contrast and the averaged ratings of the subjects. For the valence rating a negative correlation means that a larger difference in activation between meaningful and scrambled pictures lead to more negative ratings. For the arousal rating a positive correlation means that a larger difference in activation between meaningful and scrambled pictures lead to a higher arousing ratings. C, depicts the averaged ratings of negative pictures for all subjects against the fMRI contrast beta of

negative vs. scrambled pictures (Y-axis) and the regression slopes for both sexes separately.

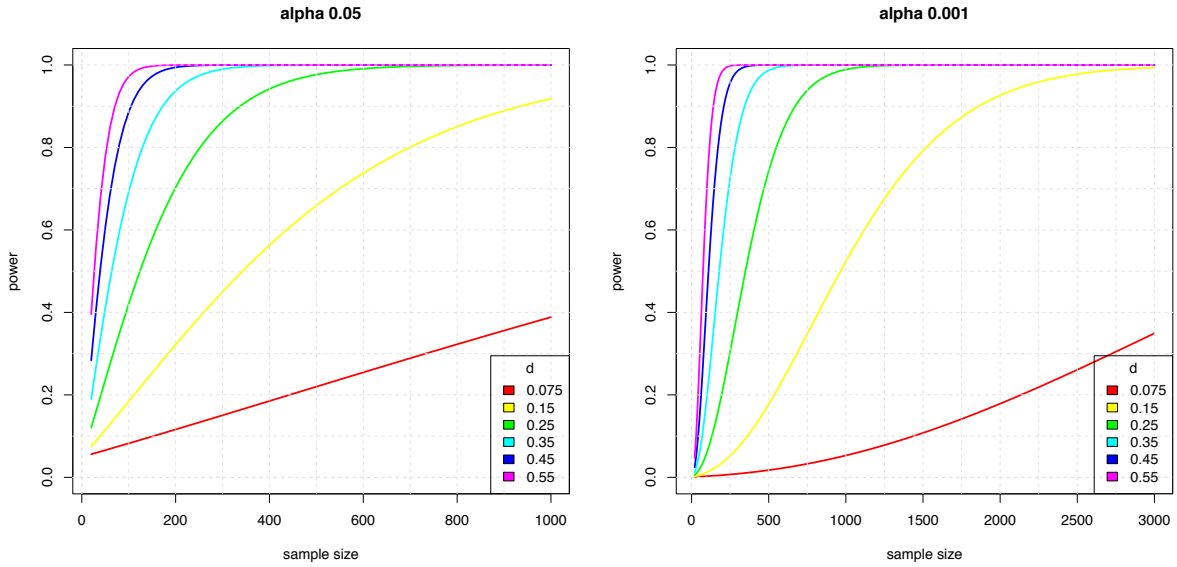

Figure 5: We calculated power-analyses for the sex effects of the behavioural data using the pwr-package (Champely, 2009) in R (R Core Team, 2012), to illustrate the necessary sample sizes to be adequately powered (80 %) to detect the reported ranges of effect-sizes in an independent sample, assuming a false-positive rate *alpha* = 0.05 (A) or *alpha* = 0.001 (B).

4.2. TESTOSTERONE LEVELS IN HEALTHY MEN ARE RELATED TO AMYGDALA REACTIVITY AND MEMORY PERFORMANCE

Ackermann, S.[*], Spalek, K.[*], Rasch, B., Gschwind, L., Coynel, D., Fastenrath, M., Papassotiropoulos, A., & de Quervain, D. J.-F. (2012). *Psychoneuroendocrinology*, *37*(9), 1417-1424.

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Testosterone levels in healthy men are related to amygdala reactivity and memory performance

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KEYWORDS
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Summary Testosterone is a steroid hormone thought to influence both emotional and cognitive functions. It is unknown, however, if testosterone also affects the interaction between these two domains, such as the emotional arousal-induced enhancement of memory. Healthy subjects ($N = 234$) encoded pictures taken from the International Affective Picture System (IAPS) during functional magnetic resonance imaging (fMRI) and underwent a free recall test 10 min after memory encoding. We show that higher endogenous testosterone levels at encoding were associated with higher arousal ratings of neutral pictures in men. fMRI analysis revealed that higher testosterone levels were related to increased brain activation in the amygdala during encoding of neutral pictures. Moreover, endogenous testosterone levels were positively correlated with the number of freely recalled neutral pictures. No such relations were found in women. These findings point to a male-specific role for testosterone in enhancing memory by increasing the biological salience of incoming information.

1. Introduction

Testosterone, a steroid hormone synthesized from cholesterol in testes, the adrenal glands and in the ovaries, plays an important role in the regulation of several central nervous system functions. In the brain, testosterone can be converted to dihydrotestosterone (DHT) and bind to androgen receptors (ARs), which are mainly located in the hippocampus (Sarrieau et al., 1990; Beyenburg et al., 2000) prefrontal

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cortex (Finley and Kritzer, 1999) and amygdala (Abdelgadir et al., 1999; Kritzer, 2004; Sarkey et al., 2008). Furthermore, testosterone can be converted to estradiol by the enzyme aromatase (Roselli et al., 2001) and bind to estradiol receptors (ERs), which are predominantly expressed in the amygdala, hypothalamus and telencephalon (Simerly et al., 1990). Because of the distribution of ARs and ERs in the brain it is not surprising that testosterone has been found to affect cognitive and emotional processes as well as social behavior (Gray et al., 2004; Janowsky, 2006).

In rodents, androgen deprivation through gonadectomy has been found to lead to impaired memory performance in hippocampus-dependent tasks (Kritzer et al., 2001; Edinger and Frye, 2004). This impairment could be prevented by testosterone replacement. However, another study did not find an effect of gonadectomy on memory and testosterone administration was impairing instead of enhancing memory performance (Harooni et al., 2008). In humans, most studies are based on data from elderly subjects. The influence of testosterone on cognitive functions in these studies is inconsistent, i.e., both positive and negative relations between testosterone and memory have been reported (Barrett-Connor et al., 1999; Perry et al., 2001; Cherrier et al., 2002, 2005; Moffat et al., 2002; Wolf and Kirschbaum, 2002; Fonda et al., 2005; Yonker et al., 2006; Hogervorst et al., 2010; Young et al., 2010).

In addition to memory, testosterone is also involved in affective behavior. A key structure in the neural network underlying affective behavior is the amygdala (Ferris et al., 2008; Ikebuchi et al., 2009; Debiec et al., 2010; Bliss-Moreau et al., 2011). In a study in mice, injection of anabolic-androgenic steroids resulted in anxious-like behaviors in novel environments, and the animals were more prone to behave aggressively (Ambar and Chiavegatto, 2009). Associations of testosterone and affective behavior were also observed in humans, particularly in relation to social dominance, aggression, and antisocial behavior (for review see van Wingen et al., 2011). The neural correlates of these behaviors include the amygdala, the medial prefrontal cortex, and the orbitofrontal cortex. Previous studies have shown a positive correlation between testosterone levels and amygdala activation in response to biologically salient stimuli in healthy subjects. In a study in healthy young males performing an emotion recognition task, the authors found significant positive correlations between amygdala activation in response to emotion specific (fearful male, fearful female and angry male) face expressions and testosterone levels (Derntl et al., 2009). In line with these findings, a study in healthy young female subjects found positive correlations between testosterone levels and activations in the amygdala, hypothalamus, temporal cortex and orbitofrontal cortex during the presentation of angry vs. happy faces (Hermans et al., 2008). In contrast, Stanton et al. (2009) observed a negative correlation between amygdala activation during viewing angry faces and endogenous testosterone levels in men. In addition to the studies, which focused on the role of testosterone in emotional processing (Hermans et al., 2008; Derntl et al., 2009; Stanton et al., 2009), the present study focused on the role of testosterone in the interaction of emotional and mnemonic processes.

Studies in animals and humans have shown that the activation of the amygdala is a key mechanism underlying the emotional arousal-induced enhancement of memory (McGaugh, 2003; Phelps and LeDoux, 2005; Anderson et al., 2006; LaBar and Cabeza, 2006; Rasch et al., 2009). In response to emotional arousal, norepinephrine (NE) is released in the amygdala (McIntyre et al., 2002), which leads to amygdala activation and reinforcing of the storage of new information in a broad network of cortical regions (McGaugh et al., 2002). In humans, pharmacologically induced increase of central noradrenergic transmission enhances memory performance (O'Carroll et al., 1999; Southwick et al., 2002; Hurlemann et al., 2005), whereas a blockade of noradrenergic transmission prevents enhanced amygdala activation in response to emotional stimuli and blocks the enhancement of memory for emotional information (Cahill et al., 1994; Strange and Dolan, 2004).

Given the relation between testosterone and the amygdala, this hormone might have an impact on memory functions by modulating amygdala reactivity. In the present study we investigate the relation between testosterone levels, emotional arousal, amygdala reactivity and memory. Ninety-six healthy young men and 138 healthy young women encoded a set of emotionally arousing and neutral pictures while fMRI data was acquired. Ten minutes after presentation, subjects underwent a free recall test of the previously seen pictures. Testosterone was measured via a saliva sample taken before picture encoding.

2. Methods

2.1. Participants

A total of 234 healthy, Caucasian, young men and women (96 men, mean age 21.74 $\pm$ 2.65 years (SD), range 18–32 years; 138 women, mean age 21.88 $\pm$ 2.75 years (SD), range 18–32 years) were included in the study. Subjects were free of any lifetime neurological or psychiatric illness, and did not take any medication at the time of the experiment. Participants filled in a questionnaire concerning their health status and were only included in the study, if they did not report any physical, neurological or mental illness. The ethics committee of the Canton of Basel approved the experiments. Written informed consent was obtained from all subjects prior to participation.

2.2. Picture task

We used an event-related design consisting of 100 trials (including 2 primacy and 2 recency trials, 24 scrambled pictures, and 72 pictures). Stimuli consisted of 72 pictures that were selected from the International Affective Picture System (IAPS; Lang et al., 1988) as well as from in-house standardized picture sets (Table S1) that allowed us to equate the pictures for visual complexity and content (e.g. human presence). On the basis of normative valence scores (from 1 to 9), pictures were assigned to emotionally negative (2.3 $\pm$ 0.6), emotionally neutral (5.0 $\pm$ 0.3) and emotionally positive (7.6 $\pm$ 0.4) conditions, resulting in 24 pictures for each emotional valence.

Four additional pictures showing neutral objects were used to control for primacy and recency effects in memory. Two of these pictures were presented in the beginning and

two at the end of the picture task. They were not included in the analysis. In addition, 24 scrambled pictures were used. The background of the scrambled pictures contained the color information of all pictures used in the experiment (except primacy and recency pictures), overlayed with a crystal and distortion filter (Adobe Photoshop CS3). In the foreground, a mostly transparent geometrical object (rectangle or ellipse of different sizes and orientations) was shown. Pictures were presented in the scanner using MR-compatible LCD goggles (Visuastim XGA, Resonance Technology, Los Angeles, CA). Eye correction was used when necessary.

2.2.1. Encoding phase

The pictures were presented for 2.5 s in a quasi-randomized order so that at maximum four pictures of the same category occurred consecutively. A fixation-cross appeared on the screen for 500 ms before each picture presentation. Trials were separated by a variable intertrial period of 9—12 s (jitter) that was equally distributed for each stimulus category. During the intertrial period, participants subjectively rated the picture showing scenes according to valence (negative = 1, neutral = 2, positive = 3) and arousal (low = 1, medium = 2, high = 3) on a three-point scale (Self Assessment Manikin, SAM) by pressing a button with a finger of their dominant hand. For scrambled pictures, participants rated form (vertical = 1, symmetric = 2 or horizontal = 3) and size (small = 1, medium = 2, large = 3) of the geometrical object in the foreground. The encoding phase of the picture had a total duration of 22 min. Participants were not told that they had to remember the pictures for later recall. Participants were instructed and trained on the picture task before being positioned in the scanner. Training consisted of presentation and rating of five pictures including scenes and scrambled pictures, which were not used during scanning.

2.2.2. Free recall phase

In the 10 min-delay between the end of picture encoding and the free recall task, subjects performed a working memory task (n-back; Gevins and Cutillo, 1993). We chose a 10 min interval because we were interested in the short-delay recall (Rasch et al., 2009). The participants were instructed to recall as many pictures as possible without any time constraints. Participants were not told how many pictures they saw in the scanner, therefore no expectation of the amount of the to be recalled pictures was mentioned to the subjects. Two independent and blind raters analyzed the recalled pictures (Cronbachs alpha was: 98% (N = 234)). Then a third independent and blind rater decided on pictures, which were rated differently.

2.3. Procedure

After receiving general information about the study and giving their written informed consent, participants were instructed and then trained on the picture task and the n-back task they later performed in the scanner. After training, they gave a saliva sample for testosterone analysis and were positioned in the scanner. Participants received earplugs and headphones to reduce scanner noise. Their head was fixated in the coil using small cushions, and they were told not to move their heads. Functional MR-images were acquired during the performance of the picture task and the n-back task (total scanning time approx. 30 min). After completing the tasks, participants left the scanner for the following free recall test of the pictures. Finally, participants filled in health and psychological questionnaires and were debriefed. The total length of the experimental procedure was approximately 3 h. Time of day of the experimental sessions varied between 1200 h and 2200 h. Participants received 25 CHF/h for participation.

2.4. fMRI data acquisition and processing

Measurements were performed on a Siemens Magnetom Verio 3 T whole body MR unit equipped with a standard twelve-channel head coil. Functional time series were acquired with a single-shot echo-planar sequence using parallel imaging (GRAPPA). We used the following acquisition parameters: TE (echo time) = 35 ms, FOV (field of view) = 22 cm, acquisition matrix = 80 $\times$ 80, interpolated to 128 $\times$ 128, voxel size: 2.8 mm $\times$ 2.8 mm $\times$ 4 mm, GRAPPA acceleration factor R = 2.0. Using a midsaggital scout image, 32 contiguous axial slices were placed along the anterior—posterior commissure (AC—PC) plane covering the entire brain with a TR = 3000 ms ($\theta = 82^{\circ}$). The first two acquisitions were discarded due to T1 saturation effects. Anatomical sequence was acquired with a radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence. For this sequence we used the following acquisition parameters: TE (echo time) = 3.37 ms, FOV (field of view) = 25.6 cm, acquisition matrix = 256 $\times$ 256 $\times$ 176, voxel size: 1 mm $\times$ 1 mm $\times$ 1 mm. Using a midsaggital scout image, 176 contiguous axial slices were placed along the anterior—posterior commissure (AC—PC) plane covering the entire brain with a TR = 2000 ms ($\theta = 8^{\circ}$).

Preprocessing and data analysis was performed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 2010a (The Mathworks Inc., Natick, MA, USA). Volumes were slice-time corrected to the first slice, realigned to the first acquired volume, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute — 152 standard atlas), and smoothed using a 8 mm full-width-at-half-maximum Gaussian kernel. A 128 s cut-off high pass filter was added to the confound partition of the design matrix to account for low-frequency drifts, and a correction for intrinsic autocorrelations was included in the analysis. For each subject, evoked hemodynamic responses to event-types were modeled with a delta (stick) function corresponding to presentation of each stimulus category (negative, positive, neutral and scrambled pictures, respectively) convolved with a canonical hemodynamic response function within the context of a general linear model (GLM). The pictures accounting for possible primacy and recency effects as well as button presses during valence and arousal ratings were modeled separately. In addition, six movement parameters from spatial realigning were included as regressors of no interest. The contrast between encoding stimuli vs. scrambled pictures was calculated individually using a fixed effects model (first level analysis). The resulting contrast parameters were then compared in relation to the endogenous testosterone levels in a random effects model (second level analysis) using a simple regression.

For testosterone-independent and -dependent analyses a statistical threshold of $p < 0.05$ (family wise error, FWE corrected) and 3 adjacent voxels ($k = 3$) was used. Given our hypothesis of a possible influence of testosterone on amygdala reactivity, we used the left and right amygdala as ROI (region of interest) where SVC (small volume correction) was applied with a threshold of $p < 0.05$ (FWE corrected). The ROI contained the left and right amygdala as defined by the Talairach atlas with the categorization in Brodmann areas (Lancaster et al., 2000), implemented in the software WFU PickAtlas v2.4 (Maldjian et al., 2003). For labeling peak voxels resulting from the whole brain analysis we used the Talairach atlas after adjusting MNI-coordinates to Talairach coordinates (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

2.5. Saliva sample

Testosterone was measured via a saliva sample using Salivette collection tubes (Sarstedt, Germany). The saliva sample was taken before picture presentation. Testosterone levels were analyzed at the Technical University of Dresden, Germany. For testosterone analysis saliva samples were centrifuged at 3000 rpm for 3 min after thawing. Concentrations of salivary free testosterone were measured using a commercially available luminescence-immuno-assay (LIA; IBL, Hamburg, Germany) with intra- and inter-assay precision of 3.24% and 3.76%, respectively. The lower sensitivity threshold of the testosterone assay is 1.8 pg/ml, the functional sensitivity threshold is 5 pg/ml. Testosterone levels in women were 95.35 ± 3.49 pg/ml (mean $\pm$ SEM), indicating that the assay was sensitive enough for women.

2.6. Statistical analysis

Behavioral data was analyzed with bivariate Pearson's correlations, repeated measurement ANOVAs or t-tests using SPSS 17.0 (SPSS, 2008). Values are presented as mean $\pm$ standard error of the mean (SEM). Due to pronounced differences in testosterone levels, men and women were analyzed separately. Our outlier criterion was ± 4 standard deviations. We did not have to exclude any of our subjects due to the outlier criterion.

3. Results

3.1. Salivary testosterone

The mean endogenous testosterone level in men (155.61 ± 4.47 pg/ml) was significantly higher than in women (95.35 ± 3.49 pg/ml, $t(232) = 10.76$, $p < 0.001$).

3.2. Valence and arousal ratings (testosterone-independent analyses)

Valence ratings differed significantly across valence categories (men: mean valence ratings for negative pictures 1.31 ± 0.27, mean valence ratings for positive pictures 2.72 ± 0.18, mean valence ratings for neutral pictures 2.10 ± 0.16; $F(2,94) = 984.44$, $p < 0.001$; women: mean valence ratings for negative pictures 1.17 ± 0.14, mean valence ratings for positive pictures 2.76 ± 0.19, mean valence ratings for neutral pictures 2.10 ± 0.17; $F(2,136) = 3162.50$, $p < 0.001$).

Arousal ratings for the different valence categories of the pictures were significantly different, with highest arousal ratings for negative pictures and lowest arousal ratings for neutral pictures (men: mean arousal rating negative pictures 2.23 ± 0.03, mean arousal rating positive pictures 1.85 ± 0.04, mean arousal rating neutral pictures 1.34 ± 0.02; $F(2,190) = 413.47$, $p < 0.001$; women: mean arousal rating negative pictures 2.40 ± 0.03, mean arousal rating positive pictures 1.95 ± 0.03, mean arousal rating neutral pictures 1.41 ± 0.03; $F(2,274) = 734.50$, $p < 0.001$). Men and women differed significantly in the arousal ratings of all valences (arousal ratings for positive pictures: $F(1,232) = 4.14$, $p < 0.05$; arousal ratings for negative pictures: $F(1,232) = 14.30$, $p < 0.001$; arousal ratings for neutral pictures: $F(1,232) = 3.95$, $p < 0.05$).

In men as well as in women, arousal ratings were significantly higher for recalled than for non-recalled pictures (women: mean arousal recalled pictures 2.05, mean arousal non-recalled pictures 1.83; $t(1,137) = 14.15$, $p < 0.001$; men: mean arousal recalled pictures 1.97, mean arousal non-recalled pictures 1.71; $t(1,95) = 14.63$, $p < 0.001$).

3.3. Brain activation during picture encoding (testosterone-independent)

Encoding of pictures of either valence as compared to baseline (i.e. scrambled pictures) activated a large network of neocortical and limbic brain regions including the frontal lobe, the temporal lobe, medial temporal lobe structures (hippocampus, parahippocampal gyrus and amygdala), the subthalamic nucleus, the cingulate gyrus, the insular cortex, the cuneus, as well as parietal and occipital regions (Tables S2–S7 and Fig. S2A–C).

A very similar activation pattern, including amygdala, hippocampus and insular cortex was found when comparing the encoding of emotional pictures (negative and positive) to the encoding of neutral pictures (Tables S8–S11 and Fig. S3A and B).

When comparing negative to positive pictures we found activation in frontal, temporal and occipital regions. Results for the positive vs. negative contrast revealed activations in the frontal, temporal, parietal lobes and in the insula (Tables S12 and S13).

All of these activation differences were very robust at significance levels of $p < 0.05$ FWE corrected for whole brain.

3.4. Brain activation related to endogenous testosterone levels

We found a positive correlation between testosterone levels and amygdala activation during encoding of neutral vs. scrambled pictures in men only (contrast: neutral pictures > scrambled pictures; Fig. 1A, left amygdala, [−25 −3 −16], 29 voxels, $t(1,94) = 4.17$, $r = 0.39$, $p(\mathrm{SVC}) = 0.002$ (FWE)). In an exploratory whole-brain analysis no suprathreshold clusters survived the significance level of $p < 0.05$ family-wise error corrected in men and women. The amygdala was robustly ($p(\mathrm{FWE}) < 0.05$) activated during processing of neutral vs.

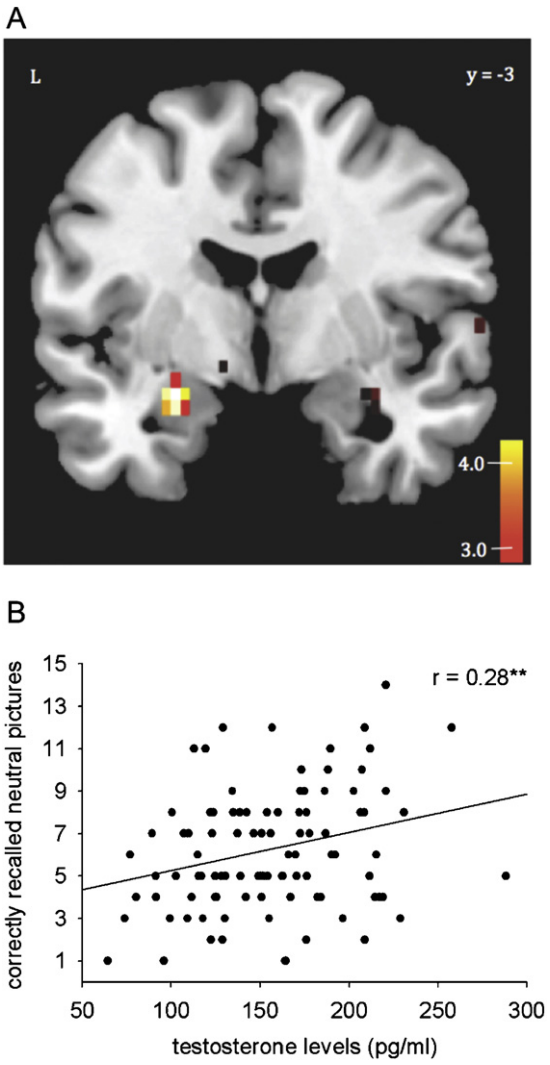

Figure 1 Correlations of testosterone levels with amygdala activity and memory performance in men. (A) Positive correlation between testosterone levels at encoding and amygdala activation during encoding of neutral pictures. Activations were overlaid on sections of a T1-weighted magnetic resonance image of SPM5, displayed at an uncorrected threshold of $p < 0.001$ and using color-coded t values. Peak activation in the amygdala was at coordinate position [−25, −3, −16], $p_{FWE\ small\ volume\ corrected} = 0.002$. (B) Correlation between testosterone levels and neutral picture memory (number of correctly recalled neutral pictures).

scrambled pictures in the testosterone-independent analysis both in men and women (Fig. S2C). There were no suprathreshold activations with decreasing endogenous testosterone levels during processing of neutral vs. scrambled pictures neither in men nor in women.

During encoding of negative vs. scrambled pictures no suprathreshold clusters with increasing nor decreasing endogenous levels of testosterone were found neither in men nor in women. During encoding of positive vs. scrambled pictures the same pattern emerged.

We additionally analyzed the contrasts negative pictures vs. neutral pictures and positive pictures vs. neutral pictures in relation to both increasing and decreasing testosterone levels. We only found a significant activation in the contrast positive pictures vs. neutral pictures with decreasing testosterone levels (left amygdala, [−25 −3 −16], 3 voxels, $t(1,94) = 4.17$, $r = 0.35$, $p(SVC) = 0.010$ (FWE)), which likely reflects the activation found in the contrast neutral pictures vs. scrambled pictures with increasing testosterone levels (same coordinates).

3.5. Memory performance (testosterone-independent analyses)

Subjects recalled more emotional than neutral pictures, (men: positive pictures 10.68 ± 0.33, negative pictures 10.73 ± 0.33, neutral pictures 6.26 ± 0.29; $F(2,190) = 175.64$, $p < 0.001$; women: positive pictures 12.73 ± 0.25, negative pictures 11.30 ± 0.26, neutral pictures 7.00 ± 0.25; $F(2,274) = 226,24$, $p < 0.001$). Women recalled significantly more positive pictures than men ($F(1,232) = 25.32$, $p < 0.001$), but men and women did not differ in the recall of negative pictures ($F(1,232) = 1.89$, $p = 0.17$). In the recall of neutral pictures men and women differed marginally ($F(1,232) = 3.77$, $p = 0.05$).

In men, amygdala activation was related to better memory performance. Brain activation in the amygdala (ROI-analysis) was higher during encoding of subsequently recalled pictures than during encoding of subsequently not recalled (forgotten) pictures (contrast: recalled pictures > not recalled pictures; left amygdala: [−19, −3, −16], $t(95) = 5.47$, $p(SVC) < 0.001$; right amygdala: [25, 3, −20], $t(95) = 3.89$, $p(SVC) = 0.005$). We found no higher activation in the amygdala for forgotten pictures compared with recalled pictures.

In women, we observed a similar pattern in the left amygdala ([−19, −6, −16], $t(137) = 5.47$, $p(SVC) = 0.004$). The right amygdala showed increased activation for subsequently recalled vs. forgotten pictures as well, but it did not survive SVC for the bilateral amygdala ([19, −6, −16], $t(137) = 2.89$, $p(SVC) = 0.068$). Again, we found no higher activation in the amygdala for forgotten pictures compared with recalled pictures.

3.6. Testosterone levels, memory performance and emotional arousal

Endogenous testosterone levels in men were significantly correlated with recall success of neutral pictures ($r = 0.28$, $p = 0.006$; Fig. 1B), but not of positive pictures ($r = 0.14$, $p = 0.18$) or negative pictures ($r = 0.13$, $p = 0.22$). The correlation with all pictures showed borderline significance ($r = 0.20$, $p = 0.05$). We did not find any significant correlations between endogenous testosterone levels and memory in women (all $p \geq 0.75$).

Looking at correlations between endogenous testosterone levels and arousal ratings in men, we found a positive correlation between endogenous testosterone levels and the arousal ratings for neutral pictures ($r = 0.22$, $p = 0.03$). Correlations between endogenous testosterone levels and arousal ratings for positive or negative pictures did not reach significance (arousal ratings positive pictures: $r = 0.16$, $p = 0.11$; arousal ratings negative pictures: $r = -0.06$, $p = 0.58$). We did not find

any significant correlations between endogenous testosterone levels and arousal levels in women (all $p \geq 0.29$).

An additional analysis dividing women in free-cycling women ($n = 50$) and women taking hormonal contraceptives ($n = 88$) suggests, that the menstrual cycle and the intake of hormonal contraceptives did not affect our findings (for memory performance of neutral pictures: interaction menstrual cycle $\times$ endogenous testosterone levels $p = 0.28$, intake of hormonal contraceptives $\times$ endogenous testosterone levels $p = 0.57$; for arousal ratings of neutral pictures: interaction menstrual cycle $\times$ endogenous testosterone levels $p = 0.23$, intake of hormonal contraceptives $\times$ endogenous testosterone levels $p = 0.36$). When conducting separate fMRI-analyses for women taking hormonal contraceptives and free cycling women, the results stayed similar.

3.7. Working memory task

We found a trend for a negative correlation between the measurement for working memory performance and endogenous testosterone levels in men ($r = -0.17$, $p = 0.09$). In women we did not find a significant correlation between testosterone levels and working memory performance ($p = 0.36$).

4. Discussion

In the present study, we investigated the role of endogenous testosterone levels in emotional processing and memory functions. We found increased emotional arousal ratings and higher amygdala reactivity to neutral pictures with increasing testosterone levels in men, but not in women. Further, increased endogenous testosterone levels in men, but not in women, were related to better memory recall of neutral pictures. These findings may point to a male-specific role for testosterone in enhancing memory by increasing the biological salience of incoming information.

The present sex-specific findings are in line with the notion that sex plays an important role in the neurobiology of emotionally influenced memory (Cahill, 2006). Sex-dependent differences with regard to cognitive functions may depend on many factors, such as type of material to be learned (e.g. spatial or verbal; Kimura, 2002) or, as in the present study, on the valence of the material. The finding that variability in acute testosterone levels in women did not correlate with memory performance suggests that the tendency of better memory for neutral information in women as compared to men is likely to be independent of sex-dependent differences in testosterone levels. Furthermore, when correcting for menstrual cycle and intake of hormonal contraceptives our behavioral and imaging findings remained the same.

Our results are in line with several previous studies examining testosterone effects on memory in men (Barrett-Connor et al., 1999; Cherrier et al., 2002, 2005; Moffat et al., 2002; Thilers et al., 2006). However, several other studies have not found any positive effects of testosterone on memory in men (Wolf et al., 2000; Hogervorst et al., 2010; Young et al., 2010). With regard to the neural underpinnings of emotional processing, Hermans et al. (2008) and Derntl et al. (2009) have reported positive correlations between blood testosterone levels and amygdala activation during processing of aversive facial expressions. In contrast, Stanton et al. (2009), found a negative correlation between amygdala activation in response to negative facial expressions and endogenous testosterone levels. These divergent results indicate that amygdala activation may depend on several factors, such as stimuli, presentation time, and instructions. Also our task differs in these parameters, which may account for the discrepancies. Furthermore, due to a pulsatile release of testosterone, a measurement of testosterone levels out of several samples would have been more reliable than a measurement out of one sample. This can be seen as a limitation of the present study.

In testosterone-independent analyses, subsequently recalled pictures induced higher amygdala activation than subsequently forgotten pictures. In the testosterone-dependent analyses, differentiating between neutral and emotional content of recalled pictures, we found a positive correlation between endogenous testosterone levels and recall of pictures with neutral content, but only in men. Importantly, endogenous testosterone levels correlated positively with increasing arousal ratings for neutral pictures as well as with higher amygdala reactivity in response to neutral pictures. These findings are in line with the idea that amygdala activation is essential in mediating the memory-enhancing effect of emotional arousal (Cahill and McGaugh, 1996; McGaugh, 2003, 2004; Phelps and LeDoux, 2005; Anderson et al., 2006; LaBar and Cabeza, 2006; Rasch et al., 2009). The phenomenon of emotional arousal-induced activation of the amygdala as a key mechanism for enhancing memory functions might also explain the lack of relation between testosterone levels, emotional arousal ratings, amygdala activation, and memory performance for emotional pictures: emotionally arousing information, such as the presented positive and negative IAPS pictures, induce per se high levels of arousal and amygdala activation, which were not further increased by high endogenous testosterone levels. Hence, no relation of testosterone levels with memory performance was found for emotional information.

Animal studies have shown that emotional arousal induces the release of norepinephrine in the amygdala, and that this neurotransmitter is crucially involved in mediating the memory-enhancing effect of emotional arousal (McGaugh et al., 2002; McIntyre et al., 2002). Several human studies corroborated these findings by showing that a pharmacologically induced increase of central noradrenergic transmission enhances memory performance (O'Carroll et al., 1999; Southwick et al., 2002; Hurlemann et al., 2005), whereas a pharmacological blockade of noradrenergic transmission prevents both amygdala activation and enhanced memory for emotionally arousing information (Cahill et al., 1994; Strange and Dolan, 2004). Based on these findings, testosterone might exert memory-enhancing effects by enhancing noradrenergic transmission within the amygdala or by stimulating a downstream mechanism. In support of a possible interaction between testosterone and the noradrenergic system it has been recently shown that testosterone and DHT have the potential to increase norepinephrine in the amygdala, although not through activation of ARs (Ely et al., 2011).

In conclusion, the present findings indicate that, in men, high testosterone levels are related to increased emotional arousal, greater amygdala reactivity and, consequently, to better memory. This emotionalizing effect of testosterone is

primarily observed for neutral information, where room for an increase in emotional arousal is present. Our data may point to a role of testosterone in enhancing memory by increasing the biological salience of incoming information. The findings further support the view of a tight interaction between emotional and cognitive processes, and that this interaction can be modulated by the gonadal hormone testosterone.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2012.01.008.

References

Abdelgadir, S.E., Roselli, C.E., Choate, J.V.A., Resko, J.A., 1999. Androgen receptor messenger ribonucleic acid in brains and pituitaries of male rhesus monkeys: studies on distribution, hormonal control, and relationship to luteinizing hormone secretion. Biol. Reprod. 60, 1251—1256.

Ambar, G., Chiavegatto, S., 2009. Anabolic-androgenic steroid treatment induces behavioral disinhibition and downregulation of serotonin receptor messenger RNA in the prefrontal cortex and amygdala of male mice. Genes Brain Behav. 8, 161—173.

Anderson, A.K., Wais, P.E., Gabrieli, J.D., 2006. Emotion enhances remembrance of neutral events past. Proc. Natl. Acad. Sci. U.S.A. 103, 1599—1604.

Barrett-Connor, E., Goodman-Gruen, D., Patay, B., 1999. Endogenous sex hormones and cognitive function in older men. J. Clin. Endocrinol. Metab. 84, 3681—3685.

Beyenburg, S., Watzka, M., Clusmann, H., Blumcke, I., Bidlingmaier, F., Elger, C.E., et al., 2000. Androgen receptor mRNA expression in the human hippocampus. Neurosci. Lett. 294, 25—28.

Bliss-Moreau, E., Toscano, J.E., Bauman, M., Mason, W.A., Amaral, D.G., 2011. Neonatal amygdala lesions alter responsiveness to objects in juvenile macaques. Neuroscience 178, 123—132.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477—484.

Cahill, L., McGaugh, J.L., 1996. The neurobiology of memory for emotional events: adrenergic activation and the amygdala. Proc. West. Pharmacol. Soc. 39, 81—84.

Cahill, L., Prins, B., Weber, M., McGaugh, J.L., 1994. Beta-adrenergic activation and memory for emotional events. Nature 371, 702—704.

Cherrier, M.M., Anawalt, B.D., Herbst, K.L., Amory, J.K., Craft, S., Matsumoto, A.M., et al., 2002. Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. J. Clin. Endocrinol. Metab. 87, 3090—3096.

Cherrier, M.M., Matsumoto, A.M., Amory, J.K., Asthana, S., Bremner, W., Peskind, E.R., et al., 2005. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. Neurology 64, 2063—2068.

Debiec, J., Diaz-Mataix, L., Bush, D.E., Doyere, V., Ledoux, J.E., 2010. The amygdala encodes specific sensory features of an aversive reinforcer. Nat. Neurosci. 13, 536—537.

Derntl, B., Windischberger, C., Robinson, S., Kryspin-Exner, I., Gur, R.C., Moser, E., et al., 2009. Amygdala activity to fear and anger in healthy young males is associated with testosterone. Psychoneuroendocrinology 34, 687—693.

Edinger, K.L., Frye, C.A., 2004. Testosterone's analgesic, anxiolytic, and cognitive-enhancing effects may be due in part to actions of its 5alpha-reduced metabolites in the hippocampus. Behav. Neurosci. 118, 1352—1364.

Ely, D., Toot, J., Salisbury, R., Ramirez, R., 2011. Androgens alter brain catecholamine content and blood pressure in the testicular feminized male rat. Clin. Exp. Hypertens. 33, 124—132.

Ferris, C.F., Stolberg, T., Kulkarni, P., Murugavel, M., Blanchard, R., Blanchard, D.C., et al., 2008. Imaging the neural circuitry and chemical control of aggressive motivation. BMC Neurosci. 9, 111.

Finley, S.K., Kritzer, M.F., 1999. Immunoreactivity for intracellular androgen receptors in identified subpopulations of neurons, astrocytes and oligodendrocytes in primate prefrontal cortex. J. Neurobiol. 40, 446—457.

Fonda, S.J., Bertrand, R., O'Donnell, A., Longcope, C., McKinlay, J.B., 2005. Age, hormones, and cognitive functioning among middle-aged and elderly men: cross-sectional evidence from the Massachusetts Male Aging Study. J. Gerontol. A: Biol. Sci. Med. Sci. 60, 385—390.

Gevins, A., Cutillo, B., 1993. Spatiotemporal dynamics of component processes in human working memory. Electroencephalogr. Clin. Neurophysiol. 87, 128—143.

Gray, P.B., Campbell, B.C., Marlowe, F.W., Lipson, S.F., Ellison, P.T., 2004. Social variables predict between-subject but not day-to-day variation in the testosterone of US men. Psychoneuroendocrinology 29, 1153—1162.

Harooni, H.E., Naghdi, N., Sepehri, H., Rohani, A.H., 2008. Intra hippocampal injection of testosterone impaired acquisition, consolidation and retrieval of inhibitory avoidance learning and memory in adult male rats. Behav. Brain Res. 188, 71—77.

Hermans, E.J., Ramsey, N.F., van Honk, J., 2008. Exogenous testosterone enhances responsiveness to social threat in the neural circuitry of social aggression in humans. Biol. Psychiatry 63, 263—270.

Hogervorst, E., Matthews, F.E., Brayne, C., 2010. Are optimal levels of testosterone associated with better cognitive function in healthy older women and men? Biochim. Biophys. Acta 1800, 1145—1152.

Hurlemann, R., Hawellek, B., Matusch, A., Kolsch, H., Wollersen, H., Madea, B., et al., 2005. Noradrenergic modulation of emotion-induced forgetting and remembering. J. Neurosci. 25, 6343—6349.

Ikebuchi, M., Hasegawa, T., Bischof, H.J., 2009. Amygdala and sociosexual behavior in male zebra finches. Brain Behav. Evol. 74, 250—257.

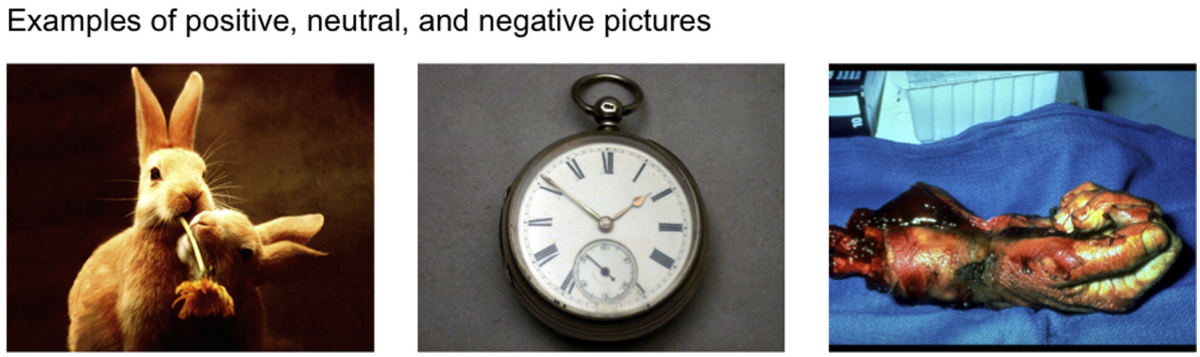
Janowsky, J.S., 2006. Thinking with your gonads: testosterone and cognition. Trends Cogn. Sci. 10, 77—82.

Kimura, D., 2002. Sex hormones influence human cognitive pattern. Neuroendocrinol. Lett. 23 (Suppl. 4), 67—77.

Kritzer, M., 2004. The distribution of immunoreactivity for intracellular androgen receptors in the cerebral cortex of hormonally

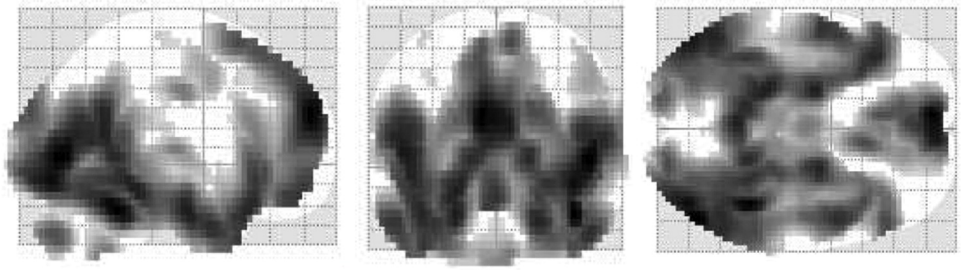
intact adult male and female rats: localization in pyramidal neurons making corticocortical connections. Cereb. Cortex 14, 268—280.
Kritzer, M.F., McLaughlin, P.J., Smirlis, T., Robinson, J.K., 2001. Gonadectomy impairs T-maze acquisition in adult male rats. Horm. Behav. 39, 167—174.
LaBar, K.S., Cabeza, R., 2006. Cognitive neuroscience of emotional memory. Nat. Rev. Neurosci. 7, 54—64.
Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., et al., 2000. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 10, 120—131.
Lang, P.J., Öhmann, A., Vaitl, D., 1988. The International Affective Picture System (slides). Center for Research in Psychophysiology, University of Florida, Gainesville, FL.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19, 1233—1239.
McGaugh, J.L., 2003. Memory and Emotion: The Making of Lasting Memories. Columbia Univ. Press, New York.
McGaugh, J.L., 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu. Rev. Neurosci. 27, 1—28.
McGaugh, J.L., McIntyre, C.K., Power, A.E., 2002. Amygdala modulation of memory consolidation: interaction with other brain systems. Neurobiol. Learn. Mem. 78, 539—552.
McIntyre, C.K., Hatfield, T., McGaugh, J.L., 2002. Amygdala norepinephrine levels after training predict inhibitory avoidance retention performance in rats. Eur. J. Neurosci. 16, 1223—1226.
Moffat, S.D., Zonderman, A.B., Metter, E.J., Blackman, M.R., Harman, S.M., Resnick, S.M., 2002. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J. Clin. Endocrinol. Metab. 87, 5001—5007.
O'Carroll, R.E., Drysdale, E., Cahill, L., Shajahan, P., Ebmeier, K.P., 1999. Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. Psychol. Med. 29, 1083—1088.
Perry, P.J., Lund, B.C., Arndt, S., Holman, T., Bever-Stille, K.A., Paulsen, J., et al., 2001. Bioavailable testosterone as a correlate of cognition, psychological status, quality of life, and sexual function in aging males: implications for testosterone replacement therapy. Ann. Clin. Psychiatry 13, 75—80.
Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48, 175—187.
Rasch, B., Spalek, K., Buholzer, S., Luechinger, R., Boesiger, P., Papassotiropoulos, A., et al., 2009. A genetic variation of the noradrenergic system is related to differential amygdala activation during encoding of emotional memories. Proc. Natl. Acad. Sci. U.S.A. 106, 19191—19196.
Roselli, C.E., Klosterman, S., Resko, J.A., 2001. Anatomic relationships between aromatase and androgen receptor mRNA expression in the hypothalamus and amygdala of adult male cynomolgus monkeys. J. Comp. Neurol. 439, 208—223.
Sarkey, S., Azcoitia, I., Garcia-Segura, L.M., Garcia-Ovejero, D., DonCarlos, L.L., 2008. Classical androgen receptors in non-classical sites in the brain. Horm. Behav. 53, 753—764.
Sarrieau, A., Mitchell, J.B., Lal, S., Olivier, A., Quirion, R., Meaney, M.J., 1990. Androgen binding-sites in human temporal cortex. Neuroendocrinology 51, 713—716.
Simerly, R.B., Chang, C., Muramatsu, M., Swanson, L.W., 1990. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. J. Comp. Neurol. 294, 76—95.
Southwick, S.M., Davis, M., Horner, B., Cahill, L., Morgan 3rd, C.A., Gold, P.E., et al., 2002. Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. Am. J. Psychiatry 159, 1420—1422.
SPSS, 2008. Rel. 17.0.1. SPSS Inc., Chicago.
Stanton, S.J., Wirth, M.M., Waugh, C.E., Schultheiss, O.C., 2009. Endogenous testosterone levels are associated with amygdala and ventromedial prefrontal cortex responses to anger faces in men but not women. Biol. Psychol. 81, 118—122.
Strange, B.A., Dolan, R.J., 2004. Beta-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. Proc. Natl. Acad. Sci. U.S.A. 101, 11454—11458.
Thilers, P.P., Macdonald, S.W., Herlitz, A., 2006. The association between endogenous free testosterone and cognitive performance: a population-based study in 35 to 90 year-old men and women. Psychoneuroendocrinology 31, 565—576.
van Wingen, G.A., Ossewaarde, L., Bäckström, T., Hermans, E.J., Fernandez, G., 2011. Gonadal hormone regulation of the emotion circuitry in humans. Neuroscience 191, 38—45.
Wolf, O.T., Kirschbaum, C., 2002. Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. Horm. Behav. 41, 259—266.
Wolf, O.T., Preut, R., Hellhammer, D.H., Kudielka, B.M., Schurmeyer, T.H., Kirschbaum, C., 2000. Testosterone and cognition in elderly men: a single testosterone injection blocks the practice effect in verbal fluency, but has no effect on spatial or verbal memory. Biol. Psychiatry 47, 650—654.
Yonker, J.E., Eriksson, E., Nilsson, L.G., Herlitz, A., 2006. Negative association of testosterone on spatial visualization in 35 to 80 year old men. Cortex 42, 376—386.
Young, L.A., Neiss, M.B., Samuels, M.H., Roselli, C.E., Janowsky, J.S., 2010. Cognition is not modified by large but temporary changes in sex hormones in men. J. Clin. Endocrinol. Metab. 95, 280—288.

Appendix A. Supplementary data

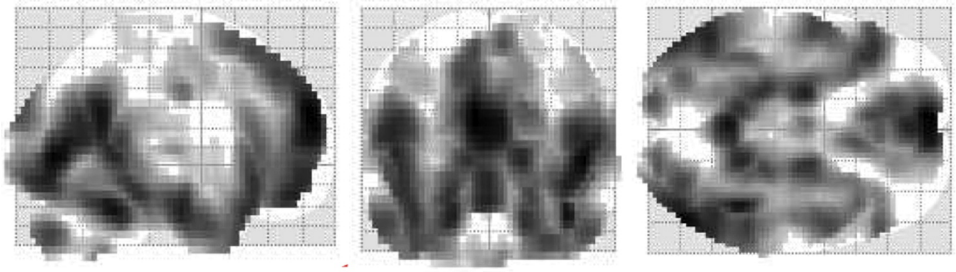


Supplementary Figure S1. Examples of IAPS pictures of the three valence categories.

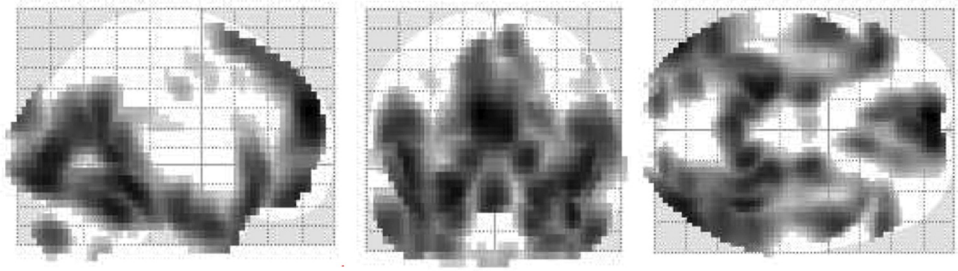
A: negative versus scrambled pictures



B: positive versus scrambled pictures

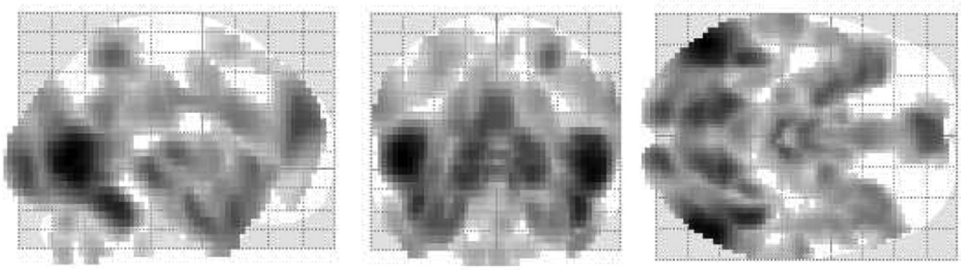


C: neutral versus scrambled pictures

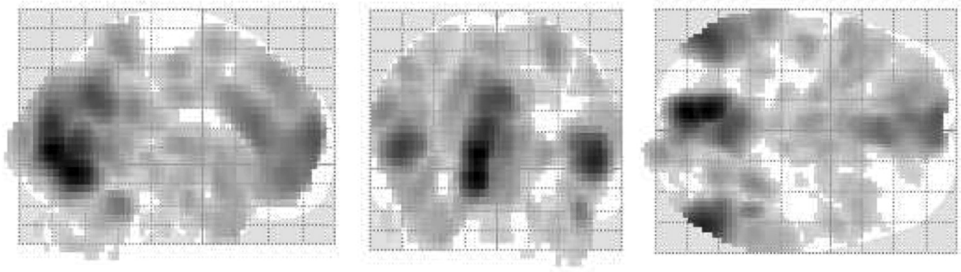


Supplementary Figure S2. Testosterone-independent whole-brain analysis, for men and women together during encoding of negative (A), positive (B) and neutral (C) pictures vs. scrambled pictures (glasbrain with sagittal, coronal and horizontal view). Data are thresholded at p(FWE) < 0.05.

A: negative versus neutral pictures



B: positive versus neutral pictures



Supplementary Figure S3. Testosterone-independent whole-brain analysis, for men and women together during encoding of negative (A) and positive (B) pictures vs. neutral pictures (glasbrain with sagittal, coronal and horizontal view). Data are thresholded at p(FWE) < 0.05.

Table S1. IAPS numbers of the included pictures

Amount	Picture valence	Picture IAPS-number
1	Positiv	1340
2	Positiv	1440
3	Positiv	1500
4	Positiv	1750
5	Positiv	2050
6	Positiv	2057
7	Positiv	2150
8	Positiv	2208
9	Positiv	2304
10	Positiv	2340
11	Positiv	2540
12	Positiv	2550
13	Positiv	4610
14	Positiv	4680
15	Positiv	5001
16	Positiv	5270
17	Positiv	5600
18	Positiv	5780
19	Positiv	5830
20	Positiv	7260
21	Positiv	8190
22	Positiv	8210
23	Positiv	8370
24	Positiv	8510

1	Negativ	1050
2	Negativ	2141
3	Negativ	2722
4	Negativ	2750
5	Negativ	3010
6	Negativ	3015
7	Negativ	3102
8	Negativ	3180
9	Negativ	3266
10	Negativ	3530
11	Negativ	6020
12	Negativ	6200
13	Negativ	6350
14	Negativ	6370
15	Negativ	9040
16	Negativ	9050
17	Negativ	9181
18	Negativ	9252
19	Negativ	9340
20	Negativ	9470
21	Negativ	9530
22	Negativ	9571
23	Negativ	9800
24	Negativ	9920

1	Neutral	2210
2	Neutral	2230
3	Neutral	2381
4	Neutral	2385
5	Neutral	2516
6	Neutral	2570
7	Neutral	2575
8	Neutral	2850
9	Neutral	4000
10	Neutral	4605
11	Neutral	5520
12	Neutral	7002
13	Neutral	7004
14	Neutral	7034
15	Neutral	7050
16	Neutral	7590
17	Neutral	in-house standardized picture
18	Neutral	in-house standardized picture
19	Neutral	in-house standardized picture
20	Neutral	in-house standardized picture
21	Neutral	in-house standardized picture
22	Neutral	in-house standardized picture
23	Neutral	in-house standardized picture
24	Neutral	in-house standardized picture

1	Training pictures	7175
2	Training pictures	5120
3	Training pictures	2682
4	Training pictures	3030
5	Training pictures	1720
6	Training pictures	2600
7	Training pictures	6211
8	Training pictures	7150
1	Primacy	7185
2	Primacy	7233
1	Recency	7006
2	Recency	7020

Table S2. Brain regions showing greater activity for negative images than for scrambled images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates *x*	*y*	*z*	*T(1,95)/ T(1,137)*	*Z*	*r*	*p*
Global activation in negative images compared to scrambled images in men										
Superior frontal gyrus	9	2123	L	*-8*	*58*	*28*	20.89	Inf	*0.91*	*<0.001*
Inferior occipital gyrus	19	9853	R	*41*	*-82*	*-8*	20.20	Inf	*0.90*	*<0.001*
Tuber		122	L	*-28*	*-80*	*-40*	12.04	Inf	*0.78*	*<0.001*
Tuber		174	R	*30*	*-80*	*-36*	11.97	Inf	*0.78*	*<0.001*
Cerebellar tonsil		48	R	*6*	*-55*	*-44*	8.63	7.39	*0.66*	*<0.001*
Cingulate gyrus	24	28	L	*-3*	*-8*	*36*	8.60	7.37	*0.66*	*<0.001*
Middle frontal gyrus	6	27	R	*52*	*6*	*48*	6.87	6.17	*0.58*	*<0.001*
Global activation in negative images compared to scrambled images in women										
Middle temporal gyrus	19	12314	R	*50*	*-80*	*4*	28.00	Inf	*0.92*	*<0.001*
Parahippocampal gyrus	35	12314	L	*-22*	*-8*	*-28*	25.21	Inf	*0.91*	*<0.001*
Superior frontal gyrus	10	2770	L	*-8*	*60*	*24*	26.67	Inf	*0.92*	*<0.001*
Superior frontal gyrus	6	2770	R	*8*	*19*	*64*	18.21	Inf	*0.84*	*<0.001*
Uvula		214	R	*28*	*-82*	*-36*	17.49	Inf	*0.83*	*<0.001*
Uvula		222	L	*-28*	*-80*	*-36*	16.09	Inf	*0.81*	*<0.001*
Cingulate gyrus	24	192	L	*-3*	*-14*	*40*	14.53	Inf	*0.78*	*<0.001*
Cerebellar tonsil		159	R	*6*	*-55*	*-48*	13.98	Inf	*0.77*	*<0.001*
Cerebellar tonsil		159	L	*-6*	*-55*	*-48*	12.84	Inf	*0.74*	*<0.001*
Middle frontal gyrus	6	206	R	*50*	*3*	*44*	10.45	Inf	*0.67*	*<0.001*
Insula	13	65	L	*-47*	*-22*	*20*	8.07	7.28	*0.57*	*<0.001*
Precentral gyrus	6	20	L	*-41*	*-19*	*64*	5.97	5.62	*0.46*	*0.001*

Table S3. Brain regions showing greater activity for scrambled images than for negative images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,95)/ T(1,137)	Z	r	p
				x	y	z				
Global activation in scrambled images compared to negative images in men										
Inferior parietal lobule	40	4630	R	44	-41	48	25.25	Inf	0.93	<0.001
			L	-41	-47	48	22.76	Inf	0.92	<0.001
Middle frontal gyrus	11	1386	R	38	55	-12	18.19	Inf	0.88	<0.001
Middle frontal gyrus	6	1709	L	-25	11	60	17.82	Inf	0.88	<0.001
Inferior temporal gyrus	37	170	L	-58	-60	-12	16.97	Inf	0.87	<0.001
Inferior temporal gyrus	20	95	R	60	-52	-16	15.41	Inf	0.85	<0.001
Cingulate gyrus	23	477	R	6	-28	28	13.49	Inf	0.81	<0.001
Medial frontal gyrus	6	477	L	-8	-28	68	6.89	6.19	0.58	<0.001
Inferior frontal gyrus	45	475	R	55	14	20	12.37	Inf	0.79	<0.001
Inferior Semi-Lunar lobule		177	L	-38	-63	-48	10.81	Inf	0.74	<0.001
Medial frontal gyrus	8	89	R	6	28	44	9.63	Inf	0.70	<0.001
Extra-Nuclear	47	177	R	33	19	0	9.53	Inf	0.70	<0.001
Culmen		97	R	30	-60	-32	9.04	7.65	0.68	<0.001
Caudate		123	L	-19	8	16	7.69	6.76	0.62	<0.001
Cingulate gyrus	24	26	R	3	3	28	7.64	6.73	0.62	<0.001
Superior temporal gyrus	41	201	L	-41	-33	8	7.28	6.47	0.60	<0.001
Cerebellar tonsil		11	L	-33	-41	-44	6.54	5.93	0.56	<0.001
Global activation in scrambled images compared to negative images in women										
Inferior parietal lobule	40	4458	L	-44	-41	48	28.96	Inf	0.93	<0.001
		4458	R	47	-41	56	27.37	Inf	0.92	<0.001
Inferior temporal gyrus	20	108	R	58	-50	-16	18.93	Inf	0.85	<0.001
Superior frontal gyrus	6	2185	L	-25	8	56	18.93	Inf	0.85	<0.001
Middle frontal gyrus	6	1245	R	28	11	60	18.27	Inf	0.84	<0.001
Middle temporal gyrus	37	161	L	-55	-58	-12	16.01	Inf	0.81	<0.001
Cingulate gyrus	23	191	R	3	-30	28	12.91	Inf	0.74	<0.001
Inferior frontal gyrus	44	118	R	55	11	16	10.20	Inf	0.66	<0.001
Cerebellar tonsil		132	L	-33	-60	-40	10.05	Inf	0.65	<0.001
Culmen		74	R	30	-63	-32	9.36	Inf	0.63	<0.001
Superior temporal gyrus	22	177	R	63	-16	0	8.21	7.39	0.58	<0.001
Caudate		34	L	-22	-38	12	6.82	6.32	0.50	<0.001
Medial frontal gyrus	8	21	R	6	28	44	6.74	6.25	0.50	<0.001

Caudate		20	R	*22*	*-36*	*12*	6.65	6.18	*0.50*	*<0.001*
Superior temporal gyrus	22	42	L	*-58*	*-16*	*0*	6.55	6.10	*0.49*	*<0.001*
Medial frontal gyrus	6	3	R	*8*	*-30*	*68*	5.28	5.03	*0.41*	*0.011*

Table S4. Brain regions showing greater activity for positive images than for scrambled images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,95)/ T(1,137)	Z	r	p
				x	y	z				
Global activation in positive images compared to scrambled images in men										
Posterior cingulated	23	9368	L	-3	-55	20	21.93	Inf	0.91	<0.001
Superior frontal gyrus	9	2538	L	-8	58	28	21.55	Inf	0.91	<0.001
Pyramis		243	R	33	-80	-40	13.81	Inf	0.82	<0.001
Cuneus	19	124	L	-16	-99	24	13.48	Inf	0.81	<0.001
Pyramis		149	L	-30	-80	-40	12.54	Inf	0.79	<0.001
Thalamus		63	R	0	-14	8	10.25	Inf	0.73	<0.001
Cingulate gyrus	24	42	L	-3	-8	36	9.69	Inf	0.71	<0.001
Cerebellar tonsil		38	R	6	-58	-48	9.01	7.63	0.68	<0.001
Middle frontal gyrus	8	45	L	-38	19	48	7.14	6.38	0.59	<0.001
Middle frontal gyrus	6	37	R	52	3	48	7.07	6.32	0.59	<0.001
Precentral gyrus	6	11	L	-38	-16	44	6.04	5.54	0.53	0.001
Anterior cingulate	25	5	R	0	3	48	5.83	5.38	0.52	0.002
Insula	13	4	R	38	-14	20	5.44	5.06	0.49	0.011
Red Nucleus		4	R	0	-19	-16	5.40	5.03	0.49	0.013
Precentral gyrus	4	4	R	44	-11	48	5.36	4.99	0.48	0.015
Global activation in positive images compared to scrambled images in women										
Middle temporal gyrus	19	11056	R	50	-80	4	25.89	Inf	0.91	<0.001
Medial frontal gyrus	10	3209	L	-6	60	24	25.83	Inf	0.91	<0.001
Tuber		252	R	28	-82	-36	18.17	Inf	0.84	<0.001
Cuneus	19	184	L	-14	-96	28	16.41	Inf	0.82	<0.001
Cingulate gyrus	24	178	L	-3	-11	40	15.16	Inf	0.79	<0.001
Cerebellar tonsil		115	R	6	-55	-48	14.02	Inf	0.77	<0.001
Cerebellar tonsil		115	L	-6	-55	-48	10.92	Inf	0.68	<0.001
Postcentral gyrus	3	131	L	-50	-14	56	9.28	Inf	0.62	<0.001
Middle frontal gyrus	6	220	R	50	3	44	9.08	Inf	0.61	<0.001
Insula	13	75	L	-41	-28	24	7.15	6.58	0.52	<0.001
Middle frontal gyrus	8	29	L	-33	19	44	7.05	6.50	0.52	<0.001
Precentral gyrus	6	4	R	30	-16	72	5.89	5.55	0.45	0.001
Precentral gyrus	4	9	R	25	-30	60	5.70	5.39	0.44	0.002
Precentral gyrus	6	5	R	25	-22	76	5.65	5.34	0.44	0.002

Anterior cingulate	25	5	R	*0*	*3*	*-7*	5.60	5.31	*0.43*	*0.003*

Table S5. Brain regions showing greater activity for scrambled images than for positive images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates *x*	*y*	*z*	*T(1,95)/ T(1,137)*	*Z*	*r*	*p*
Global activation in scrambled images compared to positive images in men										
Inferior parietal lobule	40	4720	R	*44*	*-41*	*48*	25.97	Inf	*0.94*	*<0.001*
			L	*-44*	*-41*	*52*	22.84	Inf	*0.92*	*<0.001*
Inferior frontal gyrus	9	454	L	*-50*	*11*	*24*	18.68	Inf	*0.89*	*<0.001*
Inferior temporal gyrus	37	208	L	*-58*	*-60*	*-12*	18.10	Inf	*0.88*	*<0.001*
Middle frontal gyrus	6	374	L	*-25*	*11*	*60*	16.48	Inf	*0.86*	*<0.001*
Inferior temporal gyrus	20	111	R	*60*	*-52*	*-16*	16.48	Inf	*0.86*	*<0.001*
Inferior frontal gyrus	46	1242	R	*44*	*44*	*12*	16.14	Inf	*0.86*	*<0.001*
Cingulate gyrus	23	266	R	*3*	*-28*	*28*	14.38	Inf	*0.83*	*<0.001*
Cingulate gyrus	24	266	L	*-3*	*6*	*28*	9.28	7.79	*0.69*	*<0.001*
Inferior frontal gyrus	44	246	R	*52*	*11*	*20*	13.68	Inf	*0.82*	*<0.001*
Insula	13	140	R	*33*	*22*	*0*	13.32	Inf	*0.81*	*<0.001*
Inferior frontal gyrus	46	307	L	*-47*	*41*	*12*	11.55	Inf	*0.77*	*<0.001*
Extra-Nuclear	47	48	L	*-33*	*19*	*0*	9.62	Inf	*0.70*	*<0.001*
Cerebellar tonsil		97	L	*-33*	*-60*	*-40*	9.29	7.80	*0.69*	*<0.001*
Culmen		41	R	*30*	*-60*	*-32*	8.91	7.57	*0.68*	*<0.001*
Middle temporal gyrus	21	51	R	*66*	*-11*	*-8*	7.44	6.59	*0.61*	*<0.001*
Pyramis		27	L	*-8*	*-80*	*-32*	7.20	6.41	*0.60*	*<0.001*
Cerebellar tonsil		7	L	*-30*	*-38*	*-44*	5.97	5.49	*0.52*	*0.024*
Global activation in scrambled images compared to positive images in women										
Inferior parietal lobule	40	3736	R	*47*	*-41*	*56*	27.41	Inf	*0.92*	*<0.001*
			L	*-44*	*-41*	*48*	26.92	Inf	*0.92*	*<0.001*
Lingual gyrus	17	908	R	*0*	*-88*	*0*	26.00	Inf	*0.91*	*<0.001*
Inferior temporal gyrus	20	148	R	*60*	*-52*	*-16*	21.26	Inf	*0.88*	*<0.001*
Inferior frontal gyrus	9	747	L	*-50*	*8*	*28*	18.90	Inf	*0.85*	*<0.001*
Middle occipital gyrus	19	206	L	*-52*	*-60*	*-12*	18.83	Inf	*0.85*	*<0.001*
Middle frontal gyrus	6	383	L	*-25*	*6*	*56*	18.22	Inf	*0.84*	*<0.001*
		417	R	*28*	*14*	*60*	16.21	Inf	*0.81*	*<0.001*
Middle frontal gyrus	46	585	R	*50*	*41*	*20*	15.28	Inf	*0.79*	*<0.001*
Inferior frontal gyrus	47	186	R	*33*	*22*	*-4*	12.47	Inf	*0.73*	*<0.001*
Cingulate gyrus	23	155	R	*3*	*-28*	*28*	12.19	Inf	*0.72*	*<0.001*
Inferior frontal gyrus	44	222	R	*52*	*11*	*20*	12.15	Inf	*0.72*	*<0.001*

Insula	13	111	L	*-33*	*16*	*-4*	9.86	Inf	*0.65*	*<0.001*
Cingulate gyrus	24	34	R	*3*	*3*	*28*	8.96	Inf	*0.61*	*<0.001*
Culmen		29	R	*30*	*-63*	*-32*	8.27	7.43	*0.58*	*<0.001*
Medial frontal gyrus	8	30	R	*6*	*30*	*44*	8.07	7.28	*0.57*	*<0.001*
Inferior Semi-Lunar lobule		57	L	*-33*	*-66*	*-52*	7.86	7.13	*0.56*	*<0.001*
Superior temporal gyrus	21	46	R	*63*	*-11*	*-4*	7.11	6.55	*0.52*	*<0.001*

Table S6. Brain regions showing greater activity for neutral images than for scrambled images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates *x*	*y*	*z*	*T(1,95)/ T(1,137)*	*Z*	*r*	*p*
Global activation in neutral images compared to scrambled images in men										
Middle occipital gyrus	19	7660	L	*-47*	*-85*	*4*	19.20	Inf	*0.89*	*<0.001*
			R	*41*	*-85*	*-8*	17.68	Inf	*0.88*	*<0.001*
Medial frontal gyrus	10	1842	R	*6*	*60*	*20*	18.92	Inf	*0.89*	*<0.001*
Superior frontal gyrus	9	1842	L	*-8*	*58*	*28*	18.69	Inf	*0.89*	*<0.001*
Tuber		189	R	*33*	*-80*	*-36*	12.30	Inf	*0.79*	*<0.001*
Pyramis		140	L	*-30*	*-80*	*-40*	11.58	Inf	*0.77*	*<0.001*
Caudate		21	L	*-16*	*-28*	*28*	6.95	6.23	*0.58*	*<0.001*
Cerebellar tonsil		11	R	*6*	*-55*	*-44*	6.87	6.17	*0.58*	*<0.001*
Cingulate gyrus	24	8	L	*-3*	*-11*	*40*	5.95	5.47	*0.52*	*0.001*
Global activation in neutral images compared to scrambled images in women										
Superior frontal gyrus	10	2154	L	*-8*	*60*	*28*	24.88	Inf	*0.91*	*<0.001*
Parahippocampal gyrus	36	8384	R	*25*	*-36*	*-16*	21.82	Inf	*0.88*	*<0.001*
			L	*-22*	*-38*	*-12*	21.30	Inf	*0.88*	*<0.001*
Tuber		164	R	*30*	*-82*	*-36*	16.05	Inf	*0.81*	*<0.001*
Tuber		181	L	*-28*	*-82*	*-36*	15.97	Inf	*0.81*	*<0.001*
Cerebellar tonsil		51	L	*-6*	*-55*	*-48*	9.38	Inf	*0.63*	*<0.001*
			R	*6*	*-55*	*-48*	9.15	Inf	*0.62*	*<0.001*
Cingulate gyrus	24	31	L	*-3*	*-11*	*40*	7.99	7.23	*0.57*	*<0.001*
Caudate		5	L	*-16*	*-36*	*24*	5.80	5.48	*0.45*	*0.001*
Precentral gyrus	6	3	R	*50*	*-3*	*56*	5.68	5.37	*0.44*	*0.002*
Insula	13	17	R	*25*	*-38*	*24*	5.46	5.18	*0.42*	*0.006*
Insula	13	8	L	*-36*	*-22*	*20*	5.45	5.18	*0.42*	*0.006*
Insula	13	3	R	*47*	*-16*	*20*	5.13	4.90	*0.40*	*0.021*

Table S7. Brain regions showing greater activity for scrambled images than for neutral images in men and women

Region	BA	Number of voxels	L/R	MNI coordinates *x*	*y*	*z*	*T(1,95)/ T(1,137)*	*Z*	*r*	*p*
Global activation in scrambled images compared to neutral images in men										
Inferior parietal lobule	40	5609	R	*44*	*-41*	*48*	24.80	Inf	*0.93*	*<0.001*
			L	*-47*	*-38*	*52*	21.30	Inf	*0.91*	*<0.001*
Inferior frontal gyrus	45	1627	L	*-52*	*11*	*24*	18.23	Inf	*0.88*	*<0.001*
Middle frontal gyrus	6	1627	R	*28*	*11*	*56*	15.24	Inf	*0.84*	*<0.001*
Inferior temporal gyrus	37	248	L	*-55*	*60*	*-12*	18.05	Inf	*0.88*	*<0.001*
Inferior temporal gyrus	20	133	R	*60*	*-55*	*-16*	15.83	Inf	*0.85*	*<0.001*
Inferior fontal gyrus	46	661	R	*44*	*44*	*8*	15.68	Inf	*0.85*	*<0.001*
Inferior fontal gyrus	45	264	R	*55*	*14*	*20*	13.95	Inf	*0.82*	*<0.001*
Cingulate gyrus	23	312	R	*3*	*-28*	*28*	13.19	Inf	*0.81*	*<0.001*
Cingulate gyrus	24	312	L	*-3*	*6*	*28*	10.84	Inf	*0.75*	*<0.001*
Extra-Nuclear	47	275	R	*36*	*22*	*-4*	12.73	Inf	*0.80*	*<0.001*
			L	*-33*	*19*	*0*	12.57	Inf	*0.79*	*<0.001*
Inferior frontal gyrus	46	451	L	*-44*	*41*	*12*	12.46	Inf	*0.79*	*<0.001*
Culmen		86	L	*-28*	*-63*	*-32*	9.79	Inf	*0.71*	*<0.001*
Culmen		66	R	*28*	*-60*	*-32*	9.19	7.74	*0.69*	*<0.001*
Superior temporal gyrus	21	41	R	*58*	*-14*	*-4*	7.09	6.33	*0.59*	*<0.001*
Cerebellar tonsil		12	L	*-33*	*-41*	*-44*	6.66	6.02	*0.57*	*<0.001*
Thalamus		17	L	*-14*	*-25*	*16*	6.45	5.86	*0.55*	*<0.001*
Thalamus		3	R	*16*	*-25*	*12*	5.23	4.89	*0.47*	*0.025*
Global activation in scrambled images compared to neutral images in women										
Inferior parietal lobule	40	6018	L	*-44*	*-41*	*48*	29.48	Inf	*0.93*	*<0.001*
			R	*47*	*-38*	*52*	27.66	Inf	*0.92*	*<0.001*
Middle occipital gyrus	19	278	L	*-52*	*-60*	*-12*	19.77	Inf	*0.86*	*<0.001*
Inferior frontal gyrus	9	2570	L	*-50*	*8*	*24*	19.00	Inf	*0.85*	*<0.001*
Cingulate gyrus	23	2570	R	*3*	*-28*	*28*	16.25	Inf	*0.81*	*<0.001*
Inferior temporal gyrus	20	172	R	*60*	*-52*	*-16*	18.92	Inf	*0.85*	*<0.001*
Superior frontal gyrus	6	494	R	*25*	*6*	*60*	16.31	Inf	*0.81*	*<0.001*
Middle frontal gyrus	10	674	R	*44*	*52*	*8*	14.94	Inf	*0.79*	*<0.001*
Inferior frontal gyrus	47	1024	R	*33*	*22*	*-4*	13.92	Inf	*0.77*	*<0.001*
Insula	13	1024	L	*-33*	*16*	*4*	12.59	Inf	*0.73*	*<0.001*
Inferior frontal gyrus	45	320	L	*55*	*11*	*20*	13.61	Inf	*0.76*	*<0.001*

Culmen		124	R	*28*	*-63*	*-32*	10.56	Inf	*0.67*	*<0.001*
Culmen		114	L	*-28*	*-63*	*-32*	9.76	Inf	*0.64*	*<0.001*
Cerebellar tonsil		16	L	*-30*	*-41*	*-44*	7.54	6.89	*0.54*	*<0.001*
Thalamus		47	L	*-19*	*-33*	*12*	7.30	6.70	*0.53*	*<0.001*
Inferior Semi-Lunar lobule		25	R	*19*	*-69*	*-48*	6.15	5.77	*0.47*	*<0.001*
Middle temporal gyrus	21	3	R	*66*	*-16*	*-4*	5.11	4.88	*0.40*	*0.023*

Table S8. Brain regions showing greater activity for positive images than for neutral images

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,94)/ T(1,136)	Z	r	p
				x	*y*	*z*				
Global brain activation in response to positive images compared to neutral images in men										
Cuneus	17	1326	L	*-8*	*-80*	*8*	15.87	Inf	*0.85*	*<0.001*
Middle Occipital Gyrus	19	361	R	*52*	*-72*	*4*	14.20	Inf	*0.83*	*<0.001*
Middle Temporal Gyrus	39	421	L	*-50*	*-69*	*12*	9.81	Inf	*0.71*	*<0.001*
Medial Frontal Gyrus	10	925	L	*-8*	*63*	*16*	9.64	Inf	*0.71*	*<0.001*
Fusiform Gyrus	37	67	R	*44*	*-44*	*-20*	7.86	6.88	*0.63*	*<0.001*
Postcentral Gyrus	5	67	R	*30*	*-44*	*60*	6.86	6.17	*0.58*	*<0.001*
Superior Temporal Gyrus	38	140	L	*-41*	*14*	*-16*	6.63	6.00	*0.56*	*<0.001*
Posterior Cingulate	30	18	R	*25*	*-66*	*8*	6.13	5.61	*0.53*	*0.001*
Superior Temporal Gyrus	22	20	R	*58*	*-41*	*8*	6.02	5.53	*0.53*	*0.001*
Thalamus		26	L	*-6*	*-14*	*12*	5.99	5.50	*0.53*	*0.001*
Red Nucleus		7	R	*8*	*-25*	*-4*	5.96	5.48	*0.52*	*0.001*
Parahippocampal Gyrus	34	14	R	*16*	*-3*	*-20*	5.89	5.43	*0.52*	*0.002*
Fusiform Gyrus	37	9	L	*-47*	*-55*	*-20*	5.84	5.39	*0.52*	*0.002*
Amygdala		8	L	*-19*	*-8*	*-16*	5.83	5.38	*0.52*	*0.002*
Caudate		8	L	*-6*	*8*	*8*	5.66	5.24	*0.50*	*0.004*
Superior Temporal Gyrus	22	5	L	*-55*	*8*	*4*	5.59	5.19	*0.50*	*0.006*
Mammillary Body		5	R	*6*	*-8*	*-8*	5.54	5.15	*0.50*	*0.007*
Cuneus	18	17	R	*11*	*-96*	*16*	5.54	5.14	*0.50*	*0.007*
Putamen		5	L	*-19*	*6*	*8*	5.48	5.10	*0.49*	*0.009*
Middle Frontal Gyrus	9	3	L	*-30*	*16*	*36*	5.46	5.08	*0.49*	*0.010*
Caudate		13	R	*6*	*0*	*4*	5.38	5.01	*0.49*	*0.015*
Thalamus		3	L	*-19*	*-28*	*-4*	5.34	4.96	*0.48*	*0.017*
Global brain activation in response to positive images compared to neutral images in women										
Cuneus	17	7740	L	*-11*	*-82*	*8*	21.79	Inf	*0.88*	*<0.001*
Middle Temporal Gyrus	37	1182	R	*55*	*-66*	*8*	16.30	Inf	*0.81*	*<0.001*
Middle Temporal Gyrus	39	1456	L	*-52*	*-69*	*12*	15.96	Inf	*0.81*	*<0.001*
Fusiform Gyrus	37	282	R	*44*	*-47*	*-20*	11.15	Inf	*0.69*	*<0.001*
Thalamus		719	L	*-6*	*-8*	*8*	8.82	7.81	*0.60*	*<0.001*
Inferior Frontal Gyrus	47	249	R	*44*	*16*	*-12*	7.59	6.92	*0.55*	*<0.001*
Middle Frontal Gyrus	6	75	R	*50*	*3*	*44*	7.43	6.79	*0.54*	*<0.001*
Sub-Gyral	6	64	R	*28*	*-3*	*60*	6.79	6.29	*0.50*	*<0.001*
Postcentral Gyrus	2	49	R	*33*	*-30*	*36*	6.40	5.98	*0.48*	*<0.001*
Declive		18	R	*28*	*-88*	*-32*	5.78	5.46	*0.44*	*0.001*
Middle Frontal Gyrus	8	23	L	*-30*	*22*	*48*	5.78	5.45	*0.44*	*0.001*

Postcentral Gyrus	3	5	L	*-58*	*-16*	*28*	5.44	5.17	*0.42*	*0.006*
Fusiform Gyrus	20	10	L	*-60*	*-8*	*-28*	5.41	5.14	*0.42*	*0.007*
Amygdala		6	R	*22*	*-3*	*-24*	5.39	5.12	*0.42*	*0.008*
Middle Frontal Gyrus	10	8	R	*28*	*52*	*24*	5.34	5.08	*0.42*	*0.010*
Superior Frontal Gyrus	9	8	R	*25*	*50*	*36*	5.12	4.89	*0.40*	*0.025*

Table S9. Brain regions showing greater activity for neutral images than for positive images

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,94)/ T(1,136)	Z	r	p
				x	y	z				
Global brain activation in response to neutral images compared to positive images in men										
Parahippocampal Gyrus	37	120	R	*30*	*-47*	*-12*	8.10	7.05	*0.64*	*<0.001*
Parahippocampal Gyrus	37	64	L	*-30*	*-47*	*-12*	7.23	6.44	*0.60*	*<0.001*
Lingual Gyrus	18	20	R	*11*	*-77*	*-4*	6.59	5.97	*0.56*	*<0.001*
Global brain activation in response to neutral images compared to positive images in women										
Parahippocampal Gyrus	37	197	R	*30*	*-44*	*-12*	12.58	Inf	*0.73*	*<0.001*
Hippocampus		155	L	*-28*	*-41*	*-8*	12.55	Inf	*0.73*	*<0.001*
Lingual Gyrus	18	99	R	*14*	*-74*	*-4*	10.81	Inf	*0.68*	*<0.001*
Middle Temporal Gyrus	19	65	R	*36*	*-82*	*24*	7.54	6.89	*0.54*	*<0.001*
Middle Occipital Gyrus	19	57	L	*-30*	*-91*	*12*	7.38	6.76	*0.53*	*<0.001*

Table S10. Brain regions showing greater activity for negative images than for neutral images

Region	BA	Number of voxels	L/R	MNI coordinates x	y	z	T(1,94)/ T(1,136)	Z	r	p
Global brain activation in response to negative images compared to neutral images in men										
Inferior Temporal Gyrus	37	3621	R	*52*	*-66*	*-4*	14.41	Inf	*0.83*	*<0.001*
Superior Frontal Gyrus	9	400	R	*6*	*55*	*28*	9.55	Inf	*0.70*	*<0.001*
Inferior Frontal Gyrus	47	785	L	*-33*	*16*	*-24*	9.14	7.71	*0.69*	*<0.001*
Superior Temporal Gyrus	38	275	R	*44*	*19*	*-40*	7.66	6.74	*0.62*	*<0.001*
Thalamus		23	L	*-22*	*-30*	*-4*	7.09	6.33	*0.59*	*<0.001*
Amygdala		46	R	*19*	*-3*	*-20*	7.08	6.33	*0.59*	*<0.001*
Anterior Cingulate	24	41	R	*3*	*19*	*24*	7.06	6.31	*0.59*	*<0.001*
Caudate		21	L	*-8*	*8*	*4*	6.87	6.17	*0.58*	*<0.001*
Postcentral Gyrus	3	24	R	*63*	*-16*	*32*	6.72	6.06	*0.57*	*<0.001*
Superior Parietal Lobule	7	41	R	*28*	*-52*	*60*	6.55	5.94	*0.56*	*<0.001*
Cingulate Gyrus	24	8	L	*0*	*-14*	*36*	5.91	5.44	*0.52*	*0.001*
Fusiform Gyrus	20	21	L	*-55*	*-3*	*-28*	5.83	5.38	*0.52*	*0.002*
Posterior Cingulate	30	33	L	*-3*	*-52*	*20*	5.80	5.36	*0.51*	*0.002*
Fusiform Gyrus	20	15	R	*47*	*-3*	*-32*	5.72	5.29	*0.51*	*0.003*
Superior Temporal Gyrus	22	15	R	*60*	*-47*	*12*	5.70	5.27	*0.51*	*0.004*
Postcentral Gyrus	2	8	L	*-66*	*-22*	*32*	5.65	5.23	*0.50*	*0.005*
Global brain activation in response to negative images compared to neutral images in women										
Middle Temporal Gyrus	39	15566	L	*-50*	*-72*	*8*	19.62	Inf	*0.86*	*<0.001*
Middle Frontal Gyrus	6	260	R	*50*	*3*	*44*	9.80	Inf	*0.64*	*<0.001*
Middle Frontal Gyrus	6	179	L	*-25*	*-6*	*52*	7.80	7.09	*0.56*	*<0.001*
Cerebellar Tonsil		70	R	*3*	*-58*	*-48*	7.30	6.70	*0.53*	*<0.001*

Table S11. Brain regions showing greater activity for neutral images than for negative images

Region	BA	Number of voxels	L/R	MNI coordinates x	y	z	T(1,94)/ T(1,136)	Z	r	p
Global brain activation in response to neutral images compared to negative images in men										
Inferior Parietal Lobule	40	361	R	*44*	*-52*	*48*	8.96	7.60	*0.68*	*<0.001*
Superior Temporal Gyrus		65	L	*-60*	*-8*	*0*	7.60	6.70	*0.62*	*<0.001*
Medial Frontal Gyrus	6	178	R	*8*	*-25*	*68*	7.08	6.33	*0.59*	*<0.001*
Middle Temporal Gyrus	21	60	R	*60*	*-3*	*-4*	6.67	6.03	*0.57*	*<0.001*
Insula	13	20	L	*-41*	*-30*	*16*	6.16	5.64	*0.54*	*0.001*
Middle Frontal Gyrus	8	67	R	*25*	*19*	*48*	6.14	5.62	*0.54*	*0.001*
Superior Temporal Gyrus	22	17	R	*63*	*-19*	*4*	6.07	5.57	*0.53*	*0.001*

Inferior Semi-Lunar Lobule		31	L	*-41*	*-66*	*-48*	6.00	5.51	*0.53*	*0.001*
Middle Frontal Gyrus	10	17	R	*44*	*44*	*16*	5.99	5.50	*0.53*	*0.001*
Insula	13	3	R	*33*	*-33*	*12*	5.64	5.23	*0.50*	*0.005*
Middle Frontal Gyrus	11	8	R	*38*	*55*	*-12*	5.44	5.06	*0.49*	*0.011*
Global brain activation in response to neutral images compared to negative images in women										
Inferior Parietal Lobule	40	170	R	*44*	*-60*	*48*	7.89	7.15	*0.56*	*<0.001*
Middle Frontal Gyrus	11	76	R	*41*	*55*	*-12*	6.73	6.24	*0.50*	*<0.001*
Middle Frontal Gyrus	8	92	R	*28*	*25*	*52*	6.66	6.19	*0.50*	*<0.001*
Caudate		32	L	*-22*	*-44*	*16*	6.61	6.15	*0.49*	*<0.001*
Parahippocampal Gyrus	19	18	L	*-33*	*-50*	*0*	6.48	6.04	*0.49*	*<0.001*
Medial Frontal Gyrus	6	23	R	*8*	*-30*	*68*	6.39	5.97	*0.48*	*<0.001*
Cerebellar Tonsil		21	L	*-41*	*-63*	*-44*	5.71	5.40	*0.44*	*0.002*
Middle Frontal Gyrus	46	22	R	*47*	*41*	*24*	5.64	5.34	*0.44*	*0.002*
Medial Frontal Gyrus	6	5	L	*-8*	*-30*	*64*	5.17	4.94	*0.41*	*0.017*
Caudate		3	R	*22*	*-44*	*16*	5.02	4.80	*0.40*	*0.031*

Table S12. Brain regions showing greater activity for negative images than for positive images

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,95)/ T(1,137)	Z	r	p
				x	*y*	*z*				
Global brain activation in response to negative images compared to positive images in men										
Lingual Gyrus	19	1139	R	*33*	*-63*	*-8*	12.72	Inf	*0.80*	*<0.001*
Parahippocampal Gyrus	19	1306	L	*-33*	*-55*	*-12*	11.63	Inf	*0.77*	*<0.001*
Inferior Frontal Gyrus	47	168	R	*36*	*28*	*-12*	7.89	6.90	*0.63*	*<0.001*
Medial Frontal Gyrus	9	60	R	*6*	*50*	*32*	6.98	6.25	*0.58*	*<0.001*
Inferior Frontal Gyrus	9	28	R	*44*	*11*	*24*	6.05	5.55	*0.53*	*0.001*
Inferior Frontal Gyrus	47	16	L	*-33*	*16*	*-20*	5.94	5.47	*0.52*	*0.001*
Precuneus	7	6	R	*28*	*-55*	*56*	5.64	5.22	*0.50*	*0.005*
Lateral Geniculum		4	R	*22*	*-25*	*-4*	5.29	4.94	*0.48*	*0.019*
Superior Temporal Gyrus	38	5	R	*44*	*16*	*-40*	5.26	4.91	*0.48*	*0.021*
Global brain activation in response to negative images compared to positive images in women										
Lingual Gyrus		1870	R	*19*	*-66*	*-4*	15.24	Inf	*0.79*	*<0.001*
Middle Occipital Gyrus	19	1876	L	*-33*	*-88*	*16*	14.14	Inf	*0.77*	*<0.001*
Inferior Frontal Gyrus	47	527	R	*41*	*30*	*-8*	7.90	7.16	*0.56*	*<0.001*
Middle Temporal Gyrus	21	430	L	*-52*	*8*	*-32*	7.79	7.08	*0.56*	*<0.001*
Postcentral Gyrus	1	59	L	*-63*	*-25*	*36*	7.50	6.85	*0.54*	*<0.001*
Middle Temporal Gyrus	21	60	R	*50*	*3*	*-32*	7.07	6.52	*0.52*	*<0.001*
Thalamus		43	L	*-6*	*-28*	*-4*	6.90	6.38	*0.51*	*<0.001*
Uvula		79	L	*-14*	*-80*	*-36*	6.71	6.22	*0.50*	*<0.001*
Sub-Gyral	20	67	R	*50*	*-16*	*-20*	6.67	6.19	*0.50*	*<0.001*
Precuneus	7	27	R	*25*	*-58*	*56*	6.62	6.15	*0.49*	*<0.001*
Medial Frontal Gyrus	8	107	R	*6*	*47*	*44*	6.29	5.88	*0.47*	*<0.001*
Sub-Gyral	7	43	L	*-25*	*-52*	*60*	6.25	5.85	*0.47*	*<0.001*
Postcentral Gyrus	3	17	R	*66*	*-16*	*32*	5.82	5.49	*0.45*	*0.001*
Thalamus		10	R	*6*	*-11*	*4*	5.48	5.20	*0.43*	*0.005*

Table S13. Brain regions showing greater activity for positive images than for negative images

Region	BA	Number of voxels	L/R	MNI coordinates			T(1,94)/ T(1,136)	Z	r	p
				x	y	z				
Global brain activation in response to positive images compared to negative images in men										
Lingual Gyrus	18	506	L	-8	-72	-4	10.72	Inf	0.74	<0.001
Inferior Parietal Lobule	40	194	R	47	-58	48	8.38	7.23	0.65	<0.001
Pyramis		75	L	-47	-69	-44	7.23	6.44	0.60	<0.001
Inferior Parietal Lobule	39	232	L	-50	-66	44	7.03	6.29	0.59	<0.001
Insula	13	62	R	50	-30	20	6.95	6.23	0.58	<0.001
Superior Frontal Gyrus	9	56	L	-16	47	40	6.85	6.16	0.58	<0.001
Superior Temporal Gyrus	22	71	R	60	0	-8	6.77	6.10	0.57	<0.001
Precentral Gyrus	4	41	L	-44	-14	44	6.65	6.01	0.57	<0.001
Middle Frontal Gyrus	8	17	R	33	19	52	6.34	5.77	0.55	<0.001
Anterior Cingulate	32	146	L	-8	47	-8	6.31	5.75	0.55	<0.001
Postcentral Gyrus	3	87	R	22	-33	72	6.18	5.65	0.54	<0.001
Tuber		53	R	50	-69	-36	6.14	5.62	0.54	0.001
Superior Frontal Gyrus	8	49	L	-33	22	56	6.13	5.61	0.53	0.001
Superior Frontal Gyrus	8	28	R	25	41	44	6.06	5.56	0.53	0.001
Middle Frontal Gyrus	10	23	L	-41	52	-4	5.97	5.49	0.52	0.001
Precentral Gyrus	4	24	L	-16	-28	64	5.96	5.48	0.52	0.001
Middle Frontal Gyrus	10	39	L	-41	44	28	5.88	5.42	0.52	0.002
Superior Temporal Gyrus	22	19	L	-55	-6	4	5.77	5.33	0.51	0.003
Middle Frontal Gyrus	10	4	R	41	47	16	5.64	5.22	0.50	0.005
Subcallosal Gyrus	11	3	L	-11	25	-16	5.59	5.18	0.50	0.006
Middle Frontal Gyrus	11	4	R	38	55	-8	5.54	5.14	0.50	0.007
Insula	13	6	R	38	-14	20	5.47	5.09	0.49	0.01
Global brain activation in response to positive images compared to negative images in women										
Cuneus	17	600	L	-11	-85	8	10.91	Inf	0.68	<0.001
Inferior Parietal Lobule	40	217	R	41	-60	44	9.65	Inf	0.64	<0.001
Middle Frontal Gyrus	10	377	L	-28	55	8	8.74	7.76	0.60	<0.001
Pyramis		89	R	47	-66	-44	8.70	7.74	0.60	<0.001
Inferior Parietal Lobule	40	389	L	-41	-63	44	8.35	7.50	0.58	<0.001
Caudate		160	R	25	-44	16	7.77	7.06	0.55	<0.001
Medial Frontal Gyrus	11	614	R	8	44	-12	7.47	6.83	0.54	<0.001
Cerebellar Tonsil		65	L	-44	-60	-44	7.19	6.61	0.52	<0.001
Precentral Gyrus	4	24	L	-50	-14	52	6.98	6.45	0.51	<0.001
Middle Frontal Gyrus	8	162	L	-30	16	52	6.90	6.38	0.51	<0.001
Superior Frontal Gyrus	8	117	R	25	30	52	6.70	6.22	0.50	<0.001

Middle Frontal Gyrus	9	88	L	*-44*	*28*	*36*	6.58	6.12	*0.49*	*<0.001*
Caudate		97	R	*16*	*8*	*24*	6.35	5.94	*0.48*	*<0.001*
Insula	13	8	R	*38*	*-11*	*24*	5.98	5.62	*0.46*	*<0.001*
Middle Frontal Gyrus	9	9	L	*-25*	*33*	*28*	5.76	5.44	*0.44*	*0.001*
Caudate		4	R	*11*	*19*	*0*	5.67	5.36	*0.44*	*0.002*
Caudate		10	L	*-19*	*-3*	*28*	5.61	5.31	*0.43*	*0.003*
Insula	13	9	L	*-28*	*-11*	*28*	5.39	5.12	*0.42*	*0.007*
Caudate		3	L	*-14*	*19*	*4*	5.33	5.07	*0.42*	*0.009*
Precentral Gyrus	6	17	R	*16*	*-19*	*72*	5.31	5.05	*0.41*	*0.010*
Medial Frontal Gyrus	6	8	L	*-11*	*-30*	*68*	5.25	5.00	*0.41*	*0.013*

4.3. GENETIC VARIANTS OF NTRK2 ARE ASSOCIATED WITH EMOTION PROCESSING, A WHITE-MATTER MEASURE AND DNA METHYLATION LEVELS IN HEALTHY YOUNG SUBJECTS

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Title: Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects

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Abstract

Emotional dysregulation is observed in many psychiatric diseases such as schizophrenia, mood and anxiety disorders. The neurotrophic tyrosine kinase receptor type 2 gene (*NTRK2*) has been associated with these disorders. Here we first investigated the relation between genetic variability of *NTRK2* and emotional arousal in healthy young subjects and identified a *NTRK2* single nucleotide polymorphism (SNP) associated with emotional arousal in two independent samples (n_1 = 1'171, $p_{\text{Westfall Young corrected}}$ = 0.048; n_2 = 707, $p_{\text{Westfall Young corrected}}$ = 0.036). Diffusion tensor imaging (DTI) in 342 participants revealed a whole-brain corrected ($p < 0.05$) correlation between white matter mean diffusivity (MD) and emotional arousal, as well as whole-brain corrected *NTRK2* genotype-related differences in MD. We also observed that the *NTRK2* SNP was significantly associated with *NTRK2* CpG methylation ($p < 0.003$). Our study demonstrates that genetic variability of *NTRK2* is related to emotional arousal, white matter properties and *NTRK2* methylation in healthy individuals, and might contribute to the understanding of the role of *NTRK2* in emotional dysregulation.

1. Introduction

A dysregulation of emotional processes is commonly observed in many psychiatric disorders. Specifically, more than 75% of the diagnostic categories in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are characterized by emotional dysregulation. In some psychiatric disorders, like mood or anxiety disorders, emotional dysregulation is one of the core symptoms, which give rise to the respective diagnosis (Kring & Sloan, 2009).

The International Affective Picture System (IAPS, Lang, Öhmann, & Vaitl, 1988), which consists of a large set of standardized, emotion-evoking, colour photographs covering a wide range of semantic categories, is often used in experimental studies to test and quantify emotional processes. Typically, subjects are asked to rate these pictures on two emotion dimensions, namely valence (ranging from pleasant to unpleasant) and arousal (ranging from calm to excited) (Lang, Öhmann, & Vaitl, 1988). Differences in ratings of IAPS pictures have been observed in patients with psychiatric disorders (Jayaro, de la Vega, Díaz-Marsá, Montes, & Carrasco, 2008). Several studies demonstrated altered arousal rating of IAPS pictures in schizophrenia, borderline personality disorder, major depressive disorder and substance abuse (Aguilar de Arcos et al., 2008; Aguilar de Arcos, Verdejo-García, Peralta-Ramírez, Sánchez-Barrera, & Pérez-García, 2005; Aminoff, Jensen, Lagerberg, Andreassen, & Melle, 2011; Jayaro et al., 2011; Lee et al., 2007; Strauss & Herbener, 2011).

Heritability of psychiatric disorders is generally high with heritability estimates ranging between 40%-80% (Bornovalova, Hicks, Iacono, & McGue, 2009, 2013; Cardno & Gottesman, 2000; Distel et al., 2008; Goldman, Oroszi, & Ducci, 2005; P F Sullivan, Neale, & Kendler, 2000; Sullivan, Kendler, & Neale, 2003), suggesting that genetic factors contribute to disease risk. The gene encoding the neurotrophic tyrosine kinase receptor type 2 (*NTRK2* also known as *TRKB*) has been often discussed in this context, mostly due to its involvement in the neurotrophic hypothesis of stress-related mood disorders (Duman, Heninger, & Nestler, 1997; Duman & Monteggia, 2006). Several studies have suggested a relationship between *NTRK2* and such psychiatric diseases as depression, schizophrenia, addiction, eating and anxiety disorders (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta, You, Gupta, Klistorner, & Graham, 2013; Hauger, Risbrough, Oakley, Olivares-Reyes, & Dautzenberg, 2009; Hill, 2012; Kohli et al., 2010; Mahan & Ressler, 2012; Marsden, 2013). For example, (Ernst et al., 2011) identified a deletion in a human *NTRK2* promoter and provided evidence for an

involvement of this deletion in anxiety traits. In two independent samples of depressed patients, (Kohli et al., 2010) observed an association between lifetime history of suicide attempts and a combination of several independent risk alleles within the *NTRK2* gene. In addition to psychiatric traits, some studies also point to an involvement of genetic *NTRK2* variants in brain imaging parameters, such as genotype-dependent differences in white matter properties in depressed patients (Murphy et al., 2012). In support of the genetic data, the expression pattern of TrkB in the brain, with high expression levels in different brain regions such as the occipital, temporal and frontal cerebral cortices, the putamen, and the cerebellar cortex (Barbacid, 1994; Klein, Martin-Zanca, Barbacid, & Parada, 1990; Romanczyk et al., 2002), also argues against a role for TrkB in a specific psychiatric disorder and rather points to its involvement in broad mental processes underlying psychopathology.

Because the dysregulation of emotional processes is a common characteristic of different psychiatric disorders, we hypothesized that *NTRK2* is genetically associated with emotion processing. We therefore tested the association between genetic variants of *NTRK2* and emotional arousal. The study was performed in healthy volunteers in order to avoid bias induced by the presence of psychopathology. Specifically, we quantified the arousal ratings of emotional (negative and positive) and neutral IAPS pictures in two separate samples of healthy young subjects (n_1 = 1'171, n_2 = 707). In a subsample of 342 subjects, we also analyzed genotype-dependent differences in white matter properties as assessed by diffusion tensor imaging. In this study we focused on a.) fractional anisotropy (FA), which is a measure of the directional dependence of diffusion (Basser, 1995) and reflects fiber density as well as coherence within a voxel (Christian Beaulieu, 2002), and b.) mean diffusivity (MD), which reflects the magnitude of water diffusion within a voxel and depends on the density of physical obstructions like membranes and the distribution of water molecules between different cellular compartments (Christian Beaulieu, 2002; Sen & Basser, 2005). Putative functional effects of *NTRK2* SNPs were tested by analyzing genotype-dependent methylation differences of *NTRK2* in a sub-population of 425 subjects.

2. Materials and methods

2.1. Participants

In total, we analyzed data of N = 1'878 subjects from two separate samples (a hypothesis-testing and a hypothesis-confirming sample). Overall, 64.5% of the subjects were female and the mean age was 22.96 ± 3.44 years (age-range 18-35; for information about each sample separately see supplementary IV table S1). Subjects were free of any neurological or psychiatric illness, and did not take any medication at the time of the experiment. The ethics committee of the Cantons of Basel-City and Basel-Country approved the experiments. Written informed consent was obtained from all subjects prior to participation.

2.2. Behavioral tasks

All subjects performed the identical picture task. It consisted of the presentation of 24 negative, 24 neutral and 24 positive IAPS pictures as well as pictures from in-house standardized picture sets. Subjects rated the presented pictures according to valence and arousal. For more detailed sample task and procedure description see supplementary II.

2.3. Saliva and blood DNA samples collection and isolation

Genotyping was done on the Affymetrix SNP 6.0 array, we used DNA isolated from saliva samples. Saliva samples were collected from all subjects at the time-point of the main investigation, using Oragene DNA Kit (DNA Genotek, Canada). Saliva DNA was extracted from the Oragene DNA Kit using the standard precipitation protocol recommended by the producer.

DNA methylation analysis was done on the Illumina Human methylation 450K array using DNA isolated from blood (for a detailed description see supplementary III). Blood sample collection was performed after the main investigation took place. The average time between the main investigation and re-recruitment time points was 389 days. Blood was collected using BD Vaccutainer Push Button blood collection set and 10.0 mL BD Vacutainer® Plus plastic whole blood tube, BD Hemogard™ closure with spray-coated K_2EDTA (Becton, Dickinson and Company , New Jersey, USA). Hematological analysis, including blood cell counts, was performed at the collection time point with Sysmex pocH-100*i*™ Automated Hematology Analyzer (Sysmex Co, Kobe, JP.) DNA was

isolated from the remaining fraction, upon plasma removal. The isolation was performed with QIAmp Blood Maxi Kit (Qiagen AG, Hilden, Germany), using the recommended spin protocol. The quality and concentration were assessed using gel electrophoresis, NanoDrop ND- 1000 (Thermo Scientific, Waltham, MA, USA) and fluorometry measurements (Qubit dsDNA BR Assay Kit; Invitrogen, Carlsbad, CA USA), respectively.

2.4. Genotyping and SNP selection

2.4.1. Array-based SNP genotyping

Samples were processed as described in the Genome-Wide Human SNP Nsp/ Sty 6.0 User Guide (Affymetrix). Briefly, genomic DNA concentration was determined by using a Nano-Drop ND-1000 and adjusted to 50 ng/ml in water; 250 ng of DNA was digested in parallel with ten units of Sty I and Nsp I restriction enzymes (New England Biolabs) for 2 hr at 37° C. Enzyme-specific adaptor oligonucleotides were then ligated onto the digested ends with T4 DNA Ligase for 3 hr at 16° C. After adjustment to 100 ml with water, 10 ml of the diluted ligation reactions were subjected to PCR. Three PCR reactions of 100 ml were performed for Sty-digested products and four PCR reactions for Nsp. PCR was performed with Titanium Taq DNA Polymerase (Clontech) in the presence of 4.5 mM PCR primer 002 (Affymetrix), 350 mM each dNTP (Clontech), 1 M G-C Melt (Clontech), and 13 Titanium Taq PCR Buffer (Clontech). Cycling parameters were as follows: initial denaturation at 94° C for 3 min, amplification at 94° C for 30 s, 60° C for 45 s, and extension at 68° C for 15 s repeated a total of 30 times, final extension at 68° C for 7 min. Reactions were then verified to migrate at an average size between 200–1,100 bps using 2% TBE gel electrophoresis. PCR products were combined and purified with the Filter Bottom Plate (Seahorse Bioscience) using Agencourt Magnetic Beads (Beckman Coulter). Purified PCR products were quantified on a Zenith 200rt microplate reader (Anthos-Labtec). We obtained 4–5 mg/ml on average for each sample. From this stage on, the SNP Nsp/Sty 5.0/6.0 Assay Kit (Affymetrix) was used. Around 250 mg of purified PCR products were fragmented using 0.5 units of DNase I at 37° C for 35 min. Fragmentation of the products to an average size less than 180 bps was verified using 4% TBE gel electrophoresis. After fragmentation, the DNA was end labeled with 105 units of terminal deoxynucleotidyl transferase at 37° C for 4 hr. The labeled DNA was then hybridized onto Genome-Wide Human SNP 6.0 Array at 50° C for 18 hr at 60 rpm. The hybridized array was washed, stained, and scanned according to the manufacturer's

(Affymetrix) instructions using Affymetrix GeneChip Command Console (AGCC, version 3.0.1.1214). Generation of SNP calls and Array quality control were performed using the command line programs of the Affymetrix Power Tools package (version: apt-1-14.4.1). According to the manufacturer's recommendation, Contrast QC was chosen as QC metric, using the default value of greater or equal than 0.4. All samples passing QC criteria were subsequently genotyped using the Birdseed (v2) algorithm. Mean Call Rate for all samples averaged >98.5%. This value refers to per sample (i.e., individual) call rate and ranged from 95.1% to 99.7%. Thus, no individual with an SNP call rate below 95% was included.

2.4.2. SNP selection

Generation of SNP calls and array quality control were performed using the Affymetrix Genotyping Console Software 3.0 (Affymetrix Inc.). According to the manufacturer's recommendation, contrast quality control (QC) was chosen as QC metric, using the default value of 0.4. All samples passing QC criteria were subsequently genotyped using the Birdseed (v2) algorithm. Genotypic outliers were identified and removed using Bayesian clustering algorithm (Bellenguez, Strange, Freeman, Donnelly, & Spencer, 2012). To identify and exclude subjects of non-European ancestry Bayesian clustering algorithm (Bellenguez et al., 2012) was applied on genome-wide summary statistics (for more details see supplementary I).

Single nucleotide polymorphisms (SNPs) of the *NTRK2* gene (50kb upstream and 10kb downstream) based on UCSC annotation hg19 were used for analysis. For association testing markers with genotype call rate less than 0.98, with minor allele frequency (MAF) less than 0.01, and with Hardy-Weinberg equilibrium $P < 0.05$ were excluded leading to a reduction form 135 markers to 85 markers to be analyzed.

2.5. Genetic association analysis

We used the WG-Permer software (www.wg-permer.org) for the genetic association analysis, using the analysis of variance for the quantitative phenotypes. This software corrects nominal P values for multiple testing on a permutation-based procedure according to (Westfall & Young, 1993).

Our quantitative phenotypes were mean arousal ratings per valence category (positive, negative and neutral) of IAPS pictures. Since sex- and age-related differences in emotional processing are observed (Gard & Kring, 2007; Grühn & Scheibe, 2008), we

corrected separately for these variables by using the z-transformed residuals of a linear regression.

In the hypothesis-testing sample we had originally 1'389 subjects with genetic data. After quality control we had to exclude 160 subjects (154 genetic bias and ancestry outliers and 6 subjects due to gender inconsistencies). 1'552 subjects of the hypothesis-testing sample had behavioral data. 1'171 subjects had a complete data set.

In hypothesis-confirming sample we had originally 827 subjects with genetic data. After quality control we had to exclude 104 subjects (97 genetic bias and ancestry outliers and 7 subjects due to gender inconsistencies). 1'024 subjects of hypothesis-confirming sample had behavioral data. 707 subjects had a complete data set.

2.6. DTI data acquisition and analysis

Diffusion volumes were acquired on a 3 Tesla scanner using a single-shot echo-planar sequence, and consisted of 64 diffusion-weighted volumes (b=900 s/mm2) and one unweighted volume (b=0). Diffusion data were analyzed using FSL v5.0.2 (http://www.fmrib.ox.ac.uk/fsl). Maps of FA and MD were obtained from the diffusion tensor (DT) model for further analyses. Voxel-wise statistical analysis of FA and MD maps was carried out using the Tract-Based Spatial Statistics (TBSS) toolbox of FSL (Smith et al., 2006). Voxel-wise statistical analyses were run on the skeletonized FA and MD maps using permutation-based nonparametric inference within the framework of the GLM (Nichols & Holmes, 2002), as implemented in randomize. 5'000 permutations were performed and results were considered significant for $p < 0.05$, corrected for multiple comparisons across space using the „2D" parameter settings with threshold free cluster enhancement (TFCE), which avoids using an arbitrary threshold for the initial cluster-formation (Smith & Nichols, 2009). Display of the results was done using the tbss_fill command in order to ease visualization. For more detailed information about data acquisition, processing and quantification of results see supplementary IV DTI methods. These data were only available in sample 1. Out of 707 subjects with complete data sets from the genetic association analysis results, 342 subjects had complete DTI, mean arousal rating and genotype data.

2.6.1. Genotype-independent association analysis between DTI measures and mean positive arousal rating

The linear association between mean positive arousal ratings and FA as well as MD values was tested, including age and sex as covariates.

2.6.2. Genotype-dependent association within voxels showing a significant association between MD and mean positive arousal rating

In the voxels showing a significant association between mean positive arousal ratings and MD and/or FA values we calculated a two-sample t-test to investigate genotype dependent differences.

2.6.3. *Genotype-dependent association analysis with DTI measures whole-brain wide*

FA and MD values were compared between genotype groups using a two-sample t-test, including age and sex as covariates.

2.7. Methylation analysis

On the *NTRK2* gene (50kb upstream and 10kb downstream) 15 Cytosin-phosphatidyl-Guanin (CpG)-sites were represented in the DNA methylation dataset. The data was only available in sample 2. Out of 707 subjects of with complete data sets from the genetic association analysis results, 425 subjects had complete data sets regarding methylation data, mean arousal rating and genotype data. A linear model was calculated with R (R Core Team, 2012) to test for genotype-dependent differences in methylation in these CpG-sites. Before calculation of the linear model raw beta values, representing the absolute DNA methylation levels, were logit-transformed (M-value), then z-transformed per analysis plate to account for batch effects and additionally corrected for sex and age by regressing out the residuals in order to control for possible confounding effects. Genotype groups per SNP were defined as independent variables.

We additionally calculated the correlation between methylation levels and mean positive arousal for the significant CpG-sites.

Results

2.8. Genetic association analysis

In the hypothesis-testing sample (N=1'171) five SNPs survived statistical correction for the number of tested SNP and phenotypes and showed a significant association with arousal ratings for positive pictures. The association between these SNPs and mean arousal ratings for negative or neutral pictures was not significant, neither at the corrected nor at the nominal significance level (for an overview see supplementary V table S2). The association with mean arousal ratings for positive pictures was replicated for one of the five SNPs (rs2579372) in the hypothesis-confirming sample of 707 subjects (table 1). The direction of effect and genetic model used (recessive) were the same as in the hypothesis-testing sample. Specifically, T-carriers of rs2579372 rated the positive pictures as more arousing than non T-carriers (for an overview see figure 1).

TABLE 1

FIGURE 1

2.9. Genotype-independent association between DTI measures and mean positive arousal rating

In 342 subjects we observed a whole-brain corrected ($p < 0.05$) significant negative correlation between mean positive arousal ratings and MD (i.e. higher MD values correlated with lower mean arousal ratings for positive pictures) in several tracts of the right hemisphere, amongst others in the cingulum, inferior and superior longitudinal fasciculus (see figure 1 and table 2). There was no significant (whole-brain corrected $p < 0.05$) positive association between MD and mean positive arousal ratings as well as no significant (whole-brain corrected $p < 0.05$) association between FA and mean positive arousal ratings, therefore no further analyses with FA were performed.

FIGURE 2

TABLE 2

2.10. Genotype-dependent analysis

2.10.1. *Brain-wide genotype-dependent association analysis of MD values*

We identified a number of whole-brain corrected genotype-dependent differences in MD values. Specifically, T allele-carriers (n=276) of SNP rs2579372 had higher MD values than non-carriers (n=66). These differences were mainly located bilaterally in white matter fiber bundles connecting structures of the frontal and parietal lobes (see figure 2 and table 3). There were no tracts showing significantly (whole-brain corrected) lower MD values in T allele-carriers. The brain regions showing significant correlations between MD values and arousal ratings and the regions showing genotype-dependent MD differences were to a large extent overlapping. Six out of the nine tracts showing a significant correlation between arousal ratings for positive pictures and MD had also significantly different MD values between genotype groups (see figure 3 and table 4).

2.10.2. Genotype-dependent association within voxels showing a significant association between MD and mean positive arousal rating

For the voxels showing a significant association between mean positive arousal ratings and MD we performed unpaired t-tests to investigate differences due to genotype (i.e. *NTRK2* rs2579372). There were no significant differences between the genotype groups ($t_{(340)} = -1.32$, $p = 0.19$).

FIGURE 3

TABLE 3

FIGURE 4

TABLE 4

2.11. Genotype-dependent differences in methylation levels within NTRK2

Methylation data were available for a subgroup of subjects from the hypothesis-confirming sample (N = 425). 15 CpG-sites for the defined *NTRK2* gene area (50kb upstream and 10kb downstream) were present in the DNA methylation dataset. After applying Bonferroni correction for multiple testing ($p = 0.003$), methylation levels in three CpG-sites (cg09926027, cg22402007, cg13504245) showed significant genotype-dependent differences (for an overview see supplementary V table S3 and figure S1).

Methylation at all three CpG-sites was lower in T allele-carriers of rs2579372 than in non-carriers (mean ± standard error for T allele-carriers (n = 338)/ non-carriers (n = 87); cg09926027: 0.118 ± 0.001 / 0.14 ± 0.002, p = 2.39e-09; cg22402007: 0.228 ± 0.003 / 0.246 ± 0.002, p = 0.002; cg13504245: 0.108 ± 0.001 / 0.111 ± 0.001, p = 0.003). The three CpG sites (cg09926027, cg22402007, cg13504245) are located in the proximity of the transcription start site (TSS) of *NTRK2* (http://genome.ucsc.edu/, (Kent et al., 2002)). *NTRK2* SNP rs2579372, which is positioned upstream to the TSS (distance to CpG sites: cg09926027 = 26'074 bp, cg22402007 = 23'203 bp, cg13504245 = 22'991 bp), is located in a region known to be related to active epigenetic states (Bernstein et al., 2012).

We did not observe a significant correlation between methylation levels at the three CpG sites and positive arousal ratings (all p values > 0.1).

3. Discussion

We showed that a genetic variant of *NTRK2* (rs2579372) is associated with emotional arousal in two separate samples of healthy young subjects. T allele carriers rated positive pictures as more arousing compared to non T allele carriers. Further, we identified genotype-dependent differences in methylation levels. T allele carriers had lower *NTRK2* methylation levels compared to non T allele carriers. In a genotype-independent analysis, we observed a negative correlation between mean positive arousal ratings and MD values, a white matter property. Furthermore, we observed genotype-dependent differences in MD values. Interestingly, the regions showing genotype-dependent differences in MD values largely overlapped with the regions showing significant correlations between MD values and emotional arousal.

The genotype-dependent differences in emotional arousal ratings reported herein argue in favor of an involvement of *NTRK2* in emotional processing in healthy subjects. These results also support the notion that *NTRK2* is involved in the dysregulation of emotional processes observed in psychiatric disease. Emotional arousal, specifically the rating of emotionally arousing IAPS pictures, is reportedly altered in patients with psychiatric disorders (Aguilar de Arcos et al., 2008, 2005; Aminoff et al., 2011; Jayaro et al., 2011; Lee et al., 2007; Strauss & Herbener, 2011), and several genetic associations between *NTRK2* and psychopathology have been demonstrated (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta et al., 2013; Hauger et al., 2009; Hill, 2012; Kohli et al., 2010; Mahan & Ressler, 2012; Marsden, 2013; Li et al., 2013; Lin et al., 2009; Ribases et al., 2005).

In our DTI analysis, we observed a negative correlation between mean positive arousal ratings and white matter structure properties (MD values) in tracts that are mainly part of the limbic circuits (anterior thalamic radiation, and cingulate gyrus) or form connections from other brain regions to these circuits (inferior fronto-occipital, inferior and superior longitudinal fasciculus) (Nieuwenhuys, Voogd, & Huijzen, 2008). The limbic circuitry along with its connections to other brain regions plays an essential role in emotion processing (Dalgleish, 2004). The results of our DTI analysis are in line with this evidence. In addition, several studies report significant alterations in these tracts in patients with different psychiatric disorders like obsessive compulsive disorder, bipolar disorder, autism spectrum disorder, antisocial personality disorder and schizophrenia (Fontenelle et al., 2011; Lu, Zhou, Keedy, Reilly, & Sweeney, 2011; Sundram et al., 2012; Travers et al., 2012; Zanetti et al., 2009). Interestingly, the genotype-dependent differences in MD values reported herein were regionally overlapping with the results of the correlation between arousal ratings and

MD values, and engaged areas involved in emotional processing (Dalgleish, 2004) and psychiatric disorders (Fontenelle et al., 2011; Lu et al., 2011; Sundram et al., 2012; Travers et al., 2012; Zanetti et al., 2009).

In addition to the structural differences related to *NTRK2*, we observed genotype-dependent differences in *NTRK2* methylation, specifically at the cg09926027, cg22402007, and cg13504245 CpG-sites. Given the predicted regulatory function of the affected DNA methylation site, it is possible that such genetic-dependent differences have a functional consequence with regard to gene regulation. Indeed, the epigenetic state of promoter-associated regions explains most of the variation in RNA expression (Bernstein et al., 2012).

In summary, our results suggest the involvement of *NTRK2* gene variants in emotional processing in healthy young subjects. Both the correlation of MD values with emotional arousal and the *NTRK2* genotype-dependent differences in MD values were located in white matter structures central for emotion processing in health and disease. These results may provide guidance for future studies on the role of *NTRK2* gene on the mechanisms of emotion dysregulation in psychopathology.

References

Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., López-Jiménez, A., et al. (2008). Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. *Psychopharmacology*, *198*(2), 159-66. doi:10.1007/s00213-008-1110-2

Aguilar de Arcos, F., Verdejo-García, A., Peralta-Ramírez, M. I., Sánchez-Barrera, M., & Pérez-García, M. (2005). Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug and alcohol dependence*, *78*(2), 159-67. doi:10.1016/j.drugalcdep.2004.10.010

Alonso, P., Gratacòs, M., Menchón, J. M., Saiz-Ruiz, J., Segalàs, C., Baca-García, E., Labad, J., et al. (2008). Extensive genotyping of the BDNF and NTRK2 genes define protective haplotypes against obsessive-compulsive disorder. *Biological psychiatry*, *63*(6), 619-28. doi:10.1016/j.biopsych.2007.06.020

Aminoff, S. R., Jensen, J., Lagerberg, T. V., Andreassen, O. A., & Melle, I. (2011). Decreased self-reported arousal in schizophrenia during aversive picture viewing compared to bipolar disorder and healthy controls. *Psychiatry research*, *185*(3), 309-14. doi:10.1016/j.psychres.2010.07.026

Bacanu, S.-A., Chen, J., Sun, J., Richardson, K., Lai, C.-Q., Zhao, Z., O'Donovan, M. C., et al. (2013). Functional SNPs are enriched for schizophrenia association signals. *Molecular psychiatry*. doi:10.1038/mp.2013.33

Barbacid, M. (1994). The Trk family of neurotrophin receptors. *Journal of neurobiology*, *25*(11), 1386-403. doi:10.1002/neu.480251107

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics (Oxford, England)*, *21*(2), 263-5. doi:10.1093/bioinformatics/bth457

Basser, P. J. (1995). Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in biomedicine*, *8*(7-8), 333-44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8739270

Beaulieu, C, Does, M. D., Snyder, R. E., & Allen, P. S. (1996). Changes in water diffusion due to Wallerian degeneration in peripheral nerve. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *36*(4), 627-31. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8892217

Beaulieu, Christian. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in biomedicine*, *15*(7-8), 435-55. doi:10.1002/nbm.782

Bellenguez, C., Strange, A., Freeman, C., Donnelly, P., & Spencer, C. C. A. (2012). A robust clustering algorithm for identifying problematic samples in genome-wide association studies. *Bioinformatics (Oxford, England)*, *28*(1), 134-5. doi:10.1093/bioinformatics/btr599

Benedetti, F., Giacosa, C., Radaelli, D., Poletti, S., Pozzi, E., Dallaspezia, S., Falini, A., et al. (2013). Widespread changes of white matter microstructure in obsessive-compulsive disorder: Effect of drug status. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*, *23*(7), 581-93. doi:10.1016/j.euroneuro.2012.07.002

Bernard, R., Kerman, I. A., Thompson, R. C., Jones, E. G., Bunney, W. E., Barchas, J. D., Schatzberg, A. F., et al. (2011). Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. *Molecular psychiatry*, *16*(6), 634-46. doi:10.1038/mp.2010.44

Bernstein, B. E., Birney, E., Dunham, I., Green, E. D., Gunter, C., & Snyder, M. (2012). An integrated encyclopedia of DNA elements in the human genome. *Nature*, *489*(7414), 57-74. doi:10.1038/nature11247

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2009). Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: a longitudinal twin study. *Development and psychopathology*, *21*(4), 1335-53. doi:10.1017/S0954579409990186

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2013). Longitudinal twin study of borderline personality disorder traits and substance use in adolescence: developmental change, reciprocal effects, and genetic and environmental influences. *Personality disorders*, *4*(1), 23-32. doi:10.1037/a0027178

Boulle, F., Kenis, G., Cazorla, M., Hamon, M., Steinbusch, H. W. M., Lanfumey, L., & Hove, D. L. A. V. D. (2012). TrkB inhibition as a therapeutic target for CNS-related disorders. *Progress in Neurobiology*, *98*, 197-206.

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *American journal of medical genetics*, *97*(1), 12-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10813800

Cazorla, M., Jouvenceau, A., Rose, C., Guilloux, J.-P., Pilon, C., Dranovsky, A., & Prémont, J. (2010). Cyclotraxin-B, the first highly potent and selective TrkB inhibitor, has anxiolytic properties in mice. *PloS one*, *5*(3), e9777. doi:10.1371/journal.pone.0009777

Cazorla, M., Prémont, J., Mann, A., Girard, N., Kellendonk, C., & Rognan, D. (2011). Identification of a low-molecular weight TrkB antagonist with anxiolytic and antidepressant activity in mice, *121*(5), 1846-1857. doi:10.1172/JCI43992.The

Concha, L., Gross, D. W., Wheatley, B. M., & Beaulieu, C. (2006). Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. *NeuroImage*, *32*(3), 1090-9. doi:10.1016/j.neuroimage.2006.04.187

Corporation, I. (2011). IBM SPSS Statistics for Windows. Armonk, NY: IBM Corporation.

Dalgleish, T. (2004). The emotional brain. *Nature reviews. Neuroscience*, *5*(7), 583-9. doi:10.1038/nrn1432

Deo, A. J., Huang, Y.-yu, Hodgkinson, C. A., Xin, Y., Oquendo, M. A., Dwork, A. J., Arango, V., et al. (2013). A large-scale candidate gene analysis of mood disorders: evidence of neurotrophic tyrosine kinase receptor and opioid receptor signaling dysfunction. *Psychiatric genetics*, *23*(2), 47-55. doi:10.1097/YPG.0b013e32835d7028

Distel, M. A., Trull, T. J., Derom, C. A., Thiery, E. W., Grimmer, M. A., Martin, N. G., Willemsen, G., et al. (2008). Heritability of borderline personality disorder features is similar across three countries. *Psychological medicine*, *38*(9), 1219-29. doi:10.1017/S0033291707002024

Duman, R S, Heninger, G. R., & Nestler, E. J. (1997). A molecular and cellular theory of depression. *Archives of general psychiatry*, *54*(7), 597-606. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9236543

Duman, Ronald S, & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological psychiatry*, *59*(12), 1116-27. doi:10.1016/j.biopsych.2006.02.013

Dwivedi, Y., Rizavi, H. S., Conley, R. R., Roberts, R. C., Tamminga, C. A., & Pandey, G. N. (2003). Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Archives of general psychiatry*, *60*(8), 804-15. doi:10.1001/archpsyc.60.8.804

Ernst, C., Wanner, B., Brezo, J., Vitaro, F., Tremblay, R., & Turecki, G. (2011). A deletion in tropomyosin-related kinase B and the development of human anxiety. *Biological psychiatry*, *69*(6), 604-7. doi:10.1016/j.biopsych.2010.10.008

Fontenelle, L. F., Bramati, I. E., Moll, J., Medlowicz, M. V., de Oliveira-Souza, R., & Tovar-Moll, F. (2011). White Matter Changes in OCD Revealed by Diffusion Tensor Imaging. *CNS spectrums*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21543014

Gard, M. G., & Kring, A. M. (2007). Sex differences in the time course of emotion. *Emotion (Washington, D.C.)*, *7*(2), 429-37. doi:10.1037/1528-3542.7.2.429

Goldman, D., Oroszi, G., & Ducci, F. (2005). The genetics of addictions: uncovering the genes. *Nature reviews. Genetics*, *6*(7), 521-32. doi:10.1038/nrg1635

Grühn, D., & Scheibe, S. (2008). Age-related differences in valence and arousal ratings of pictures from the International Affective Picture System (IAPS): do ratings become more extreme with age? *Behavior research methods*, *40*(2), 512-21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18522062

Gupta, V. K., You, Y., Gupta, V. B., Klistorner, A., & Graham, S. L. (2013). TrkB Receptor Signalling: Implications in Neurodegenerative, Psychiatric and Proliferative Disorders. *International journal of molecular sciences*, *14*(5), 10122-42. doi:10.3390/ijms140510122

Hauger, R. L., Risbrough, V., Oakley, R. H., Olivares-Reyes, J. A., & Dautzenberg, F. M. (2009). Role of CRF receptor signaling in stress vulnerability, anxiety, and depression. *Annals of the New York Academy of Sciences*, *1179*, 120-43. doi:10.1111/j.1749-6632.2009.05011.x

Hill, R. a. (2012). Interaction of sex steroid hormones and brain-derived neurotrophic factor-tyrosine kinase B signalling: relevance to schizophrenia and depression. *Journal of neuroendocrinology*, *24*(12), 1553-61. doi:10.1111/j.1365-2826.2012.02365.x

Jayaro, C., De La Vega, I., Bayon-Palomino, C., Díaz-Marsá, M., Montes, A., Tajima, K., López-Ibor, J. J., et al. (2011). Depressive-type emotional response pattern in impulsive-aggressive patients with borderline personality disorder. *Journal of affective disorders*, *135*(1-3), 37-42. doi:10.1016/j.jad.2011.06.040

Jayaro, C., de la Vega, I., Díaz-Marsá, M., Montes, a, & Carrasco, J. L. (2008). [The use of the International Affective Picture System for the study of affective dysregulation in mental disorders]. *Actas españolas de psiquiatría*, *36*(3), 177-82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18478458

Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., Zahler, A. M., & Haussler, D. (2002). The human genome browser at UCSC. *Genome research*, *12*(6), 996-1006. doi:10.1101/gr.229102. Article published online before print in May 2002

Klein, R., Lamballe, F., Bryant, S., & Barbacid, M. (1992). The trkB tyrosine protein kinase is a receptor for neurotrophin-4. *Neuron*, *8*(5), 947-56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1375038

Klein, R., Martin-Zanca, D., Barbacid, M., & Parada, L. F. (1990). Expression of the tyrosine kinase receptor gene trkB is confined to the murine embryonic and adult nervous system. *Development (Cambridge, England)*, *109*(4), 845-50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2171894

Klein, R., Nanduri, V., Jing, S. A., Lamballe, F., Tapley, P., Bryant, S., Cordon-Cardo, C., et al. (1991). The trkB tyrosine protein kinase is a receptor for brain-derived neurotrophic factor and neurotrophin-3. *Cell*, *66*(2), 395-403. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2710095&tool=pmcentrez&rendertype=abstract

Kohli, M. a, Salyakina, D., Pfennig, A., Lucae, S., Horstmann, S., Menke, A., Kloiber, S., et al. (2010). Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. *Archives of general psychiatry*, *67*(4), 348-59. doi:10.1001/archgenpsychiatry.2009.201

Kring, A. M., & Sloan, D. M. (2009). *Emotion Regulation and Psychopathology: A Transdiagnostic Approach to Etiology and Treatment* (p. 461). New York: The Guilford Press. Retrieved from http://www.amazon.com/Emotion-Regulation-Psychopathology-Transdiagnostic-Treatment/dp/1606234501

Kubera, M., Obuchowicz, E., Goehler, L., Brzeszcz, J., & Maes, M. (2011). In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. *Progress in neuro-psychopharmacology & biological psychiatry*, *35*(3), 744-59. doi:10.1016/j.pnpbp.2010.08.026

Lang, P. J., Öhmann, A., & Vaitl, D. (1988). *The International Affective Picture System (slides)*. Gainesville, FL.

Lee, B.-T., Seong Whi Cho, Hyung Soo Khang, Lee, B.-C., Choi, I.-G., Lyoo, I. K., & Ham, B.-J. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in neuro-psychopharmacology & biological psychiatry*, *31*(7), 1487-92. doi:10.1016/j.pnpbp.2007.06.030

Li, Z., Zhang, Y., Wang, Z., Chen, J., Fan, J., Guan, Y., Zhang, C., et al. (2013). The role of BDNF, NTRK2 gene and their interaction in development of treatment-resistant depression: data from multicenter, prospective, longitudinal clinic practice. *Journal of psychiatric research*, *47*(1), 8-14. doi:10.1016/j.jpsychires.2012.10.003

Lin, E., Hong, C.-J., Hwang, J.-P., Liou, Y.-jay, Yang, C.-hong, Cheng, D., & Tsai, S.-J. (2009). Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. *Rejuvenation research*, *12*(6), 387-93. doi:10.1089/rej.2009.0871

Liu, X., Chan, C.-B., Qi, Q., Xiao, G., Luo, H. R., He, X., & Ye, K. (2012). Optimization of a small tropomyosin-related kinase B (TrkB) agonist 7,8-dihydroxyflavone active in mouse models of depression. *Journal of medicinal chemistry*, *55*(19), 8524-37. doi:10.1021/jm301099x

Lu, L. H., Zhou, X. J., Keedy, S. K., Reilly, J. L., & Sweeney, J. A. (2011). White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar disorders*, *13*(7-8), 604-13. doi:10.1111/j.1399-5618.2011.00958.x

Mahan, A. L., & Ressler, K. J. (2012). Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends in neurosciences*, *35*(1), 24-35. doi:10.1016/j.tins.2011.06.007

Marsden, W. N. (2013). Synaptic plasticity in depression: molecular, cellular and functional correlates. *Progress in neuro-psychopharmacology & biological psychiatry*, *43*, 168-84. doi:10.1016/j.pnpbp.2012.12.012

Maussion, G., Yang, J., Yerko, V., Barker, P., Mechawar, N., Ernst, C., & Turecki, G. (2012). Regulation of a truncated form of tropomyosin-related kinase B (TrkB) by Hsa-miR-185* in frontal cortex of suicide completers. *PloS one*, *7*(6), e39301. doi:10.1371/journal.pone.0039301

Murphy, M. L., Carballedo, A., Fagan, A. J., Morris, D., Fahey, C., Meaney, J., & Frodl, T. (2012). Neurotrophic tyrosine kinase polymorphism impacts white matter connections in patients with major depressive disorder. *Biological psychiatry*, *72*(8), 663-70. doi:10.1016/j.biopsych.2012.04.015

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping*, *15*(1), 1-25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11747097

Nieuwenhuys, R., Voogd, J., & Huijzen, C. (2008). *The Human Central Nervous System*. Berlin, Heidelberg: Springer Berlin Heidelberg. doi:10.1007/978-3-642-96477-0

Rantamäki, T., & Castrén, E. (2008). Targeting TrkB neurotrophin receptor to treat depression. *Expert opinion on therapeutic targets*, *12*(6), 705-15. doi:10.1517/14728222.12.6.705

Ribases, M., Gratacos, M., Badia, A., Jimenez, L., Solano, R., Vallejo, J., Fernandez-Aranda, F., et al. (2005). Contribution of NTRK2 to the genetic susceptibility to anorexia nervosa, harm avoidance and minimum body mass index. *Molecular psychiatry*, *10*(9), 851-60. doi:10.1038/sj.mp.4001670

Romanczyk, T. B., Weickert, C. S., Webster, M. J., Herman, M. M., Akil, M., & Kleinman, J. E. (2002). Alterations in trkB mRNA in the human prefrontal cortex throughout the lifespan. *The European journal of neuroscience*, *15*(2), 269-80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11849294

Saarelainen, T., Hendolin, P., Lucas, G., Koponen, E., Sairanen, M., MacDonald, E., Agerman, K., et al. (2003). Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *23*(1), 349-57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12514234

Schaub, M. A., Boyle, A. P., Kundaje, A., Batzoglou, S., & Snyder, M. (2012). Linking disease associations with regulatory information in the human genome. *Genome research*, *22*(9), 1748-59. doi:10.1101/gr.136127.111

Sen, P. N., & Basser, P. J. (2005). A model for diffusion in white matter in the brain. *Biophysical journal*, *89*(5), 2927-38. doi:10.1529/biophysj.105.063016

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487-505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83-98. doi:10.1016/j.neuroimage.2008.03.061

Soontornniyomkij, B., Everall, I. P., Chana, G., Tsuang, M. T., Achim, C. L., & Soontornniyomkij, V. (2011). Tyrosine kinase B protein expression is reduced in the cerebellum of patients with bipolar disorder. *Journal of affective disorders*, *133*(3), 646-54. doi:10.1016/j.jad.2011.04.044

Soppet, D., Escandon, E., Maragos, J., Middlemas, D. S., Reid, S. W., Blair, J., Burton, L. E., et al. (1991). The neurotrophic factors brain-derived neurotrophic factor and neurotrophin-3 are ligands for the trkB tyrosine kinase receptor. *Cell*, *65*(5), 895-903. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1645620

Strauss, G. P., & Herbener, E. S. (2011). Patterns of emotional experience in schizophrenia: differences in emotional response to visual stimuli are associated with clinical presentation and functional outcome. *Schizophrenia research*, *128*(1-3), 117-23. doi:10.1016/j.schres.2011.01.010

Sullivan, P F, Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *The American journal of psychiatry*, *157*(10), 1552-62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11007705

Sullivan, Patrick F, Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry*, *60*(12), 1187-92. doi:10.1001/archpsyc.60.12.1187

Sundram, F., Deeley, Q., Sarkar, S., Daly, E., Latham, R., Craig, M., Raczek, M., et al. (2012). White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex; a journal devoted to the study of the nervous system and behavior*, *48*(2), 216-29. doi:10.1016/j.cortex.2011.06.005

Thompson Ray, M., Weickert, C. S., Wyatt, E., & Webster, M. J. (2011). Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. *Journal of psychiatry & neuroscience : JPN*, *36*(3), 195-203. doi:10.1503/jpn.100048

Travers, B. G., Adluru, N., Ennis, C., Tromp, D. P. M., Destiche, D., Doran, S., Bigler, E. D., et al. (2012). Diffusion tensor imaging in autism spectrum disorder: a review. *Autism research : official journal of the International Society for Autism Research*, *5*(5), 289-313. doi:10.1002/aur.1243

Tripp, A., Oh, H., Guilloux, J.-P., Martinowich, K., Lewis, D. a, & Sibille, E. (2012). Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *The American journal of psychiatry*, *169*(11), 1194-202. doi:10.1176/appi.ajp.2012.12020248

Westfall, P. H., & Young, S. S. (1993). *Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment (Wiley Series in Probability and Statistics)*. Wiley-Interscience. Retrieved from http://www.amazon.com/Resampling-Based-Multiple-Testing-Adjustment-Probability/dp/0471557617

Zanetti, M. V., Jackowski, M. P., Versace, A., Almeida, J. R. C., Hassel, S., Duran, F. L. S., Busatto, G. F., et al. (2009). State-dependent microstructural white matter changes in bipolar I depression. *European archives of psychiatry and clinical neuroscience*, *259*(6), 316-28. doi:10.1007/s00406-009-0002-8

Figures and Tables

Table 1

Hypothesis-testing sample											
					homozygous minor allele carriers			**heterozygous and major allele carriers**			
SNP	**Model**	***p* nominal**	**WY[1] (SNP+PT)**	**minor/ major allele**	**N**	**MEAN**	**SD[2]**	**N**	**MEAN**	**SD[2]**	**Total N**
rs2579372	Carrier T	0.0003	0.0478	C/T	268	-0.18	0.95	893	0.06	1.00	1'161
rs1212171	Carrier A	0.0003	0.0446	G/A	261	-0.19	0.95	910	0.06	1.00	1'171
Hypothesis-confirming sample											
					homozygous minor allele carriers			**heterozygous and major allele carriers**			
SNP	**Model**	***p* nominal**	**WY[1](SNP)**	**minor/ major allele**	**N**	**MEAN**	**SD[2]**	**N**	**MEAN**	**SD[2]**	**Total N**
rs2579372	Carrier T	0.0141	0.0356	C/T	134	-0.20	1.01	573	0.03	0.98	707
rs1212171	Carrier A	0.0283	0.0639	G/A	131	-0.18	1.01	576	0.02	0.99	707

[1]WY=Westfall Young for single nucleotide polymorphism (SNP) and phenotype (PT), [2]SD=standard deviation

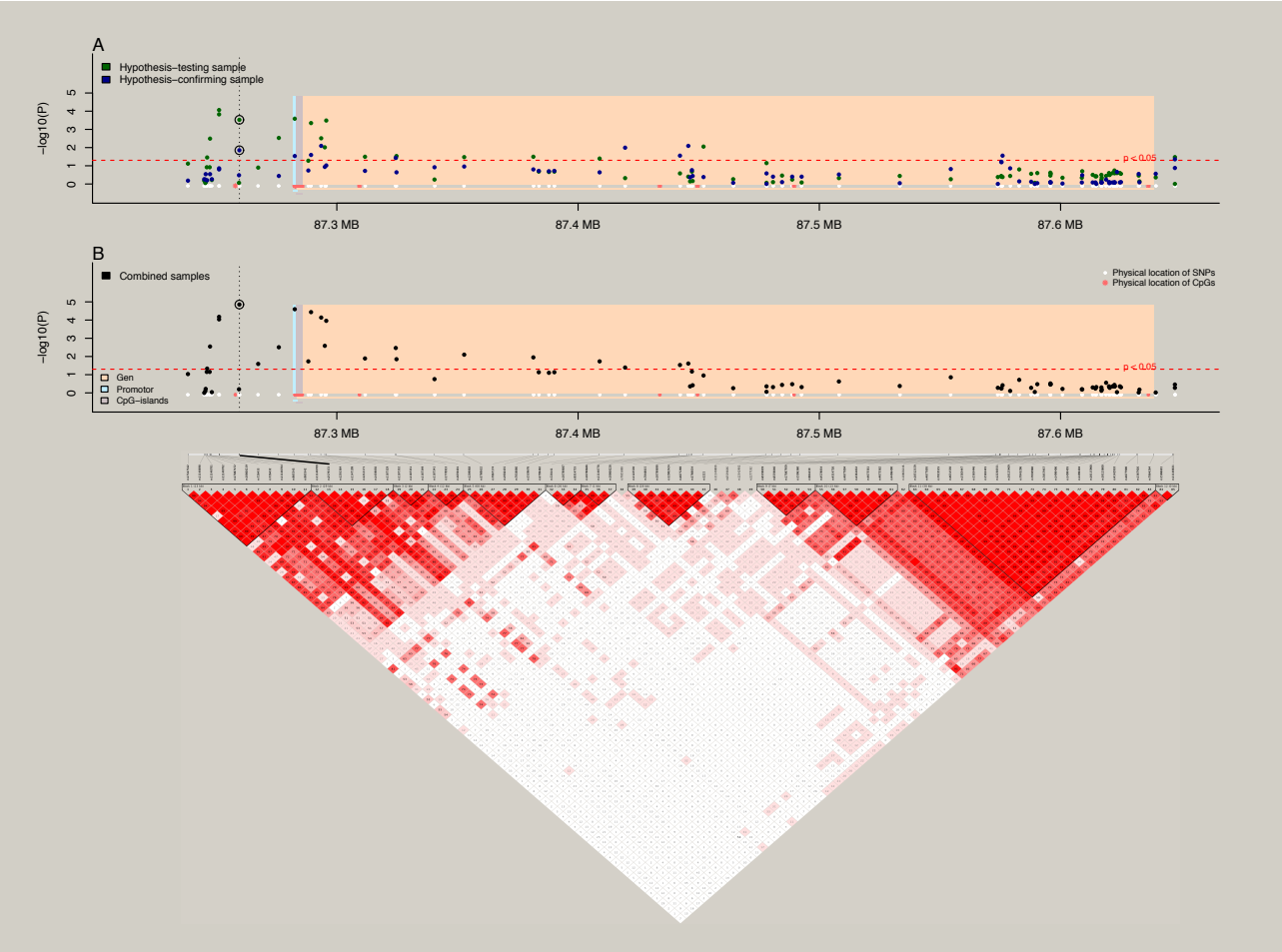


Figure 1: Association between 85 NTRK2 gene SNPs (recessive model) and mean positive arousal ratings **A)** for the hypothesis-testing and –confirming sample separately as well as **B)** in the combined sample. In A) and B) the significant SNP rs2579372 is marked by a circle. Bellow the LD structure of the 85 NTRK2 gene SNPs hypothesis-testing sample is depicted. The position of the SNP rs2579372 is emphasized.

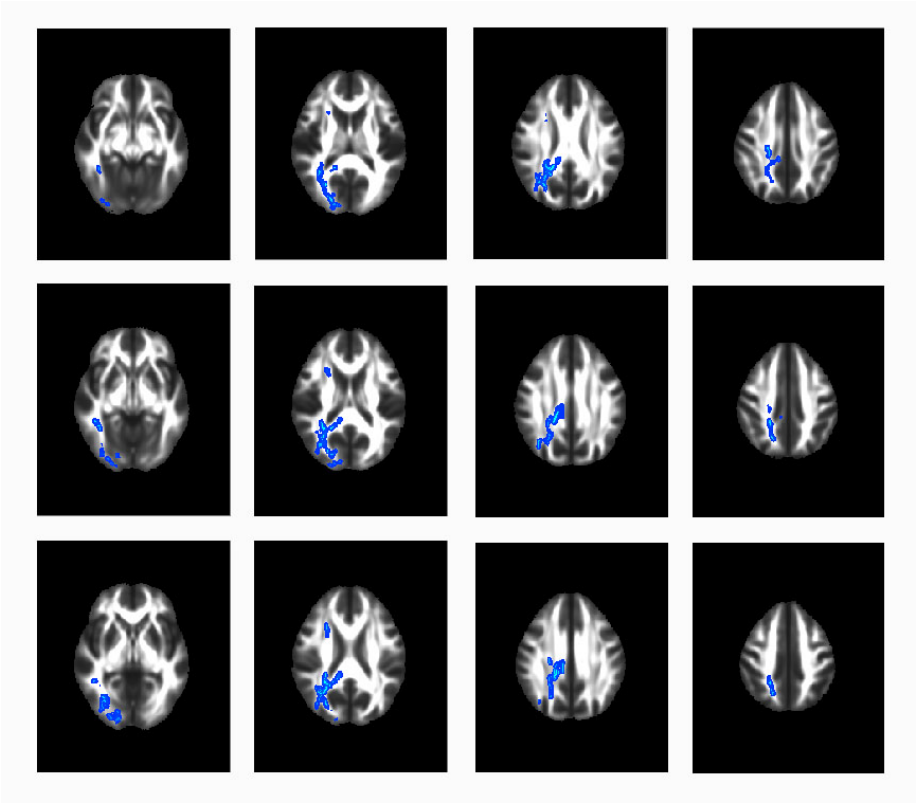


Figure 2: Genotype-independent association between mean positive arousal ratings and mean diffusivity (whole-brain corrected ($p < 0.05$)).

Table 2

Region	Hemisphere[1]	min. corrected p – value[2]	min. uncorrected p – value[3]
Anterior thalamic radiation	R	0.0444	0.0018
Cingulum (cingulate gyrus)	R	0.0348	0.0036
Corticospinal tract	R	0.0400	0.0036
Forceps major		0.0348	0.0016
Forceps minor		0.0460	0.0022
Inferior fronto-occipital fasciculus	R	0.0324	0.0026
Inferior longitudinal fasciculus	R	0.0356	0.0030
Superior longitudinal fasciculus (temporal part)	R	0.0334	0.0044
Superior longitudinal fasciculus	R	0.0334	0.0044

Regions showing a significant whole-brain corrected ($p < 0.05$) association between mean positive arousal ratings and MD values.

[1]L = left hemisphere, R = right hemisphere

[2]represents the smallest whole-brain corrected p – value in the tract

[3]represents the smallest uncorrected p – value in the tract

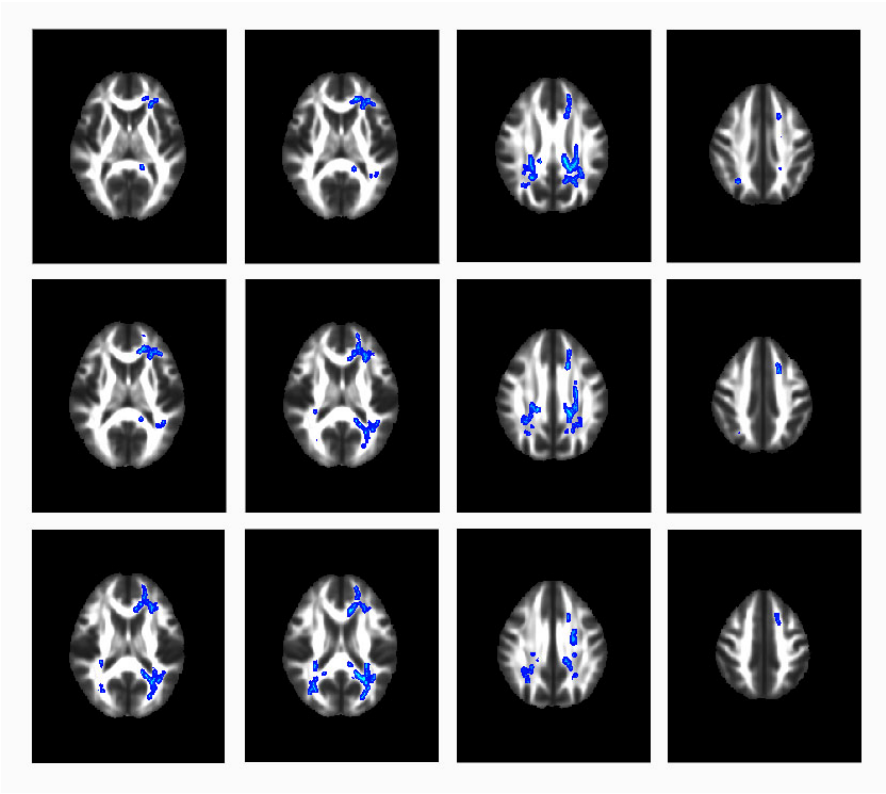
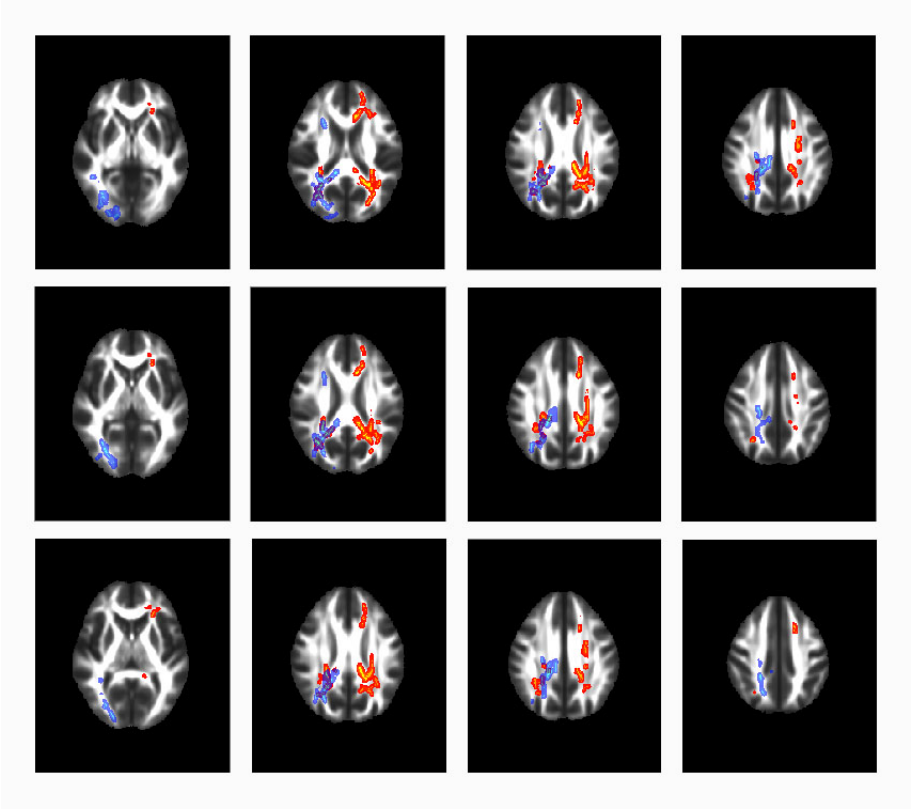


Figure 3: Regions with significant whole-brain corrected ($p < 0.05$) genotype-dependent differences in MD.

Table 3

Region	Hemisphere[1]	min. corrected *p* – value[2]	min. uncorrected *p* – value[3]
Anterior thalamic radiation	L	0.0366	0.0026
Cingulum (cingulate gyrus)	L	0.0436	0.0036
Corticospinal tract	L	0.0366	0.0054
	R	0.0490	0.0048
Forceps_major		0.0440	0.0024
Forceps_minor		0.0454	0.0030
Inferior fronto-occipital fasciculus	L	0.0456	0.0018
	R	0.0482	0.0060
Inferior longitudinal fasciculus	L	0.0454	0.0016
Superior longitudinal fasciculus (temporal part)	L	0.0456	0.0046
	R	0.0494	0.0066
Superior longitudinal fasciculus	L	0.0454	0.0026
	R	0.0494	0.0038
Uncinate fasciculus	L	0.0460	0.0042

Regions showing genotype-dependent whole-brain corrected ($p < 0.05$) significant differences in MD.
[1]L = left hemisphere, R = right hemisphere
[2]represents the smallest whole-brain corrected p – value in the tract
[3]represents the smallest uncorrected p – value in the tract



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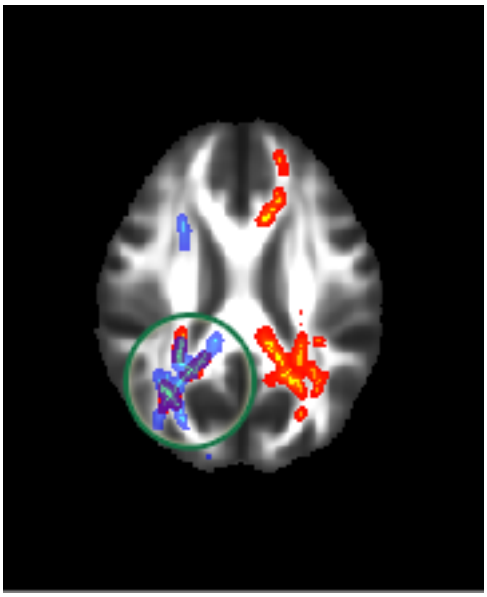

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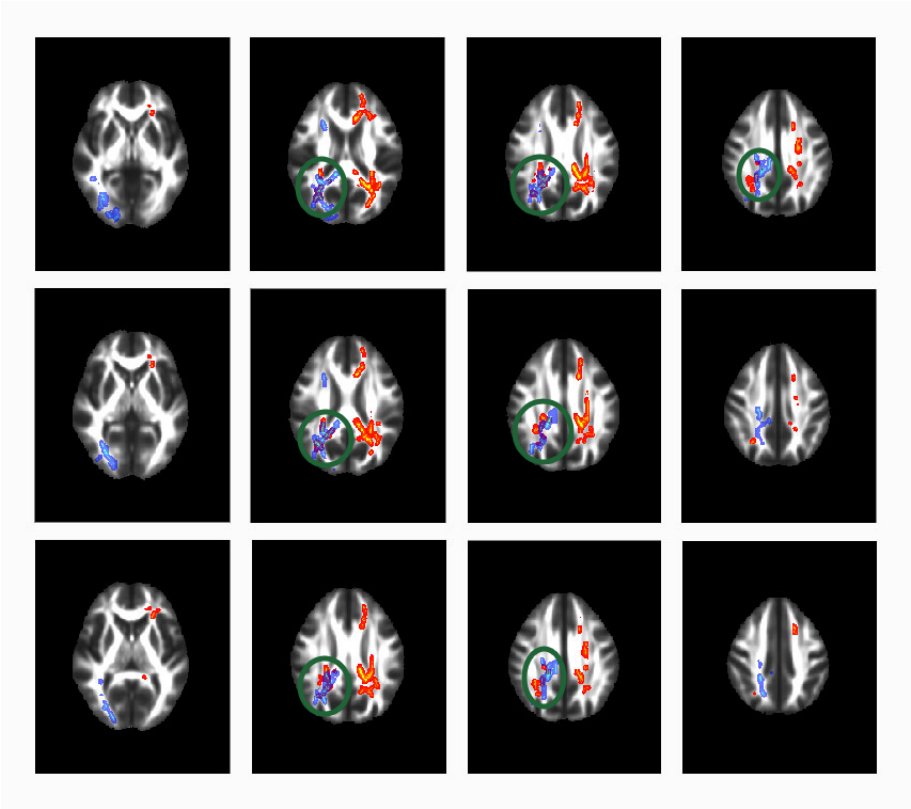

Figure 4: In blue are represented tracts showing a significant whole-brain corrected ($p < 0.05$) genotype-independent association between MD and mean positive arousal rating. In red significant whole-brain corrected ($p < 0.05$) genotype-dependent differences in MD are displayed.

Table 4

Region		MD mean positive arousal rating		MD genotype-dependent	
	Hemisphere[1]	min. corrected *p* – value[2]	min. uncorrected *p* – value[3]	min. corrected *p* – value[2]	min. uncorrected *p* – value[3]
Anterior thalamic radiation	R	0.0444	0.0018	-	-
Cingulum (cingulate gyrus)	R	0.0348	0.0036	-	-
Corticospinal tract	R	0.0400	0.0036	0.0490	0.0048
Forceps major		0.0348	0.0016	0.0440	0.0024
Forceps minor		0.0460	0.0022	0.0454	0.0030
Inferior fronto-occipital fasciculus	R	0.0324	0.0026	0.0482	0.0060
Inferior longitudinal fasciculus	R	0.0356	0.0030	-	-
Superior longitudinal fasciculus (temporal part)	R	0.0334	0.0044	0.0494	0.0066
Superior longitudinal fasciculus	R	0.0334	0.0044	0.0494	0.0038

Regions showing a significant whole-brain corrected ($p < 0.05$) association between mean positive arousal ratings and MD values (MD mean positive arousal rating) and significant genotype-dependent differences (MD genotype-dependent) in these regions in MD.

[1]L = left hemisphere, R = right hemisphere

[2]represents the smallest whole-brain corrected p – value in the tract

[3]represents the smallest uncorrected p – value in the tract

Supplementary

Supplementary I: Sample quality control with bayesian clustering algorithm

Within each center Bayesian Clustering Algorithm (Bellenguez, Strange, Freeman, Donnelly, & Spencer, 2012) was applied on genome-wide summary statistics to identify and exclude atypical samples. Considering a combination of two summary statistics, the algorithm infers each sample's posterior probability to belong to the outliers' class. A first outlier assessment was based on genome-wide call rate and heterozygosis rates, for which extreme values may be indicative of a genotyping bias. The second assessment aimed at identifying subjects with unusual ancestry according to the majority of the samples. This was done by projecting the samples' genotypic data on the two first PCA components inferred from HapMap data using YRI, CEU and CHB-JPT populations. Samples were also checked for consistency between genetically inferred and self-reported gender.

Supplementary II: Procedure and task description

The experiment of both samples, the hypothesis-testing and a hypothesis-confirming sample, was conducted in Basel. The task used here for analyses was in both samples the identical one. In the discovery sample subjects performed two times on that task. To ensure comparability between the samples we used the first performance on the task in that sample. The procedures of the two samples were different.

1. Picture task

We used an event-related design consisting of 100 trials (including 2 primacy and 2 recency trials, 24 scrambled pictures, and 72 pictures). Stimuli consisted of 72 pictures that were selected from the IAPS (IAPS; (Lang, Öhmann, & Vaitl, 1988)) as well as from in-house standardized picture sets that allowed us to equate the pictures for visual complexity and content (e.g. human presence). On the basis of normative valence scores (from 1 to 9), pictures were assigned to emotionally negative (2.3 ± 0.6), emotionally positive (7.6 ± 0.4), and emotionally neutral (5.0 ± 0.3) conditions, resulting in 24 pictures for each emotional valence. Four additional IAPS pictures showing neutral objects were used to control for primacy and recency effects in memory. Two of these pictures were presented in the beginning and two at the end of the picture task. They were not included in the analysis. In addition to the IAPS pictures, 24 scrambled pictures

were used. The scrambled pictures consisted of a colored background, containing the colour information of all pictures used in the experiment (except primacy and recency pictures), overlaid with a crystal and distortion filter (Adobe Photoshop CS3). In the foreground, a mostly transparent geometrical object (rectangle or ellipse of different sizes and orientations) was shown.

The pictures were presented for 2.5 seconds in a quasi-randomized order so that at maximum four pictures of the same category occurred consecutively. A fixation-cross appeared on the screen for 500 ms before each picture presentation. Trials were separated by a variable intertrial period (period between appearance of a picture and the next fixation cross) of 9 - 12 seconds (jitter). During the intertrial period, participants subjectively rated the picture showing scenes according to valence (positive=1, neutral=2, negative=3; recoded afterwards to positive=1, neutral=0, negative=-1) and arousal (high=1, medium=2, low=3; recoded afterwards to high=3, medium=2, low=1) on a three-point scale (Self Assessment Manikin, SAM) by pressing a button with a finger of their dominant hand. For scrambled pictures, participants rated form (vertical=1, symmetric=2, horizontal=3) and size (small=1, medium=2, large=3) of the geometrical object in the foreground. The total duration of the picture task was 20 minutes. Participants were instructed and trained on the picture task before the task performance. Training consisted of presentation and rating of five pictures including scenes and scrambled pictures, which were not used during the main task.

Hypothesis-testing sample

2. Procedure

The experiments were conducted on three dates, where two were on two consecutive days. After performing on the first day on a memory task, participants received instructions and were trained on the picture task, amongst others. After training, participants performed on the picture task for 20 minutes. On the third date, participants completed again the picture task (20 minutes) with a new set of emotional and neutral pictures. On last two dates, participants filled in health and psychological questionnaires and were debriefed at the end of the experiment. The total length of the experiment procedure was approximately 6 to 6.5 hours. Participants received 25.- CHF/h for participation.

Hypothesis-confirming sample

1. Procedure

After receiving general information about the study and giving their written informed consent, participants were instructed and then trained on the picture task they later performed. After having performed on some tasks, subjects went in the MR-scanner for the diffusion tensor imaging (DTI) measurements. Scans were acquired for 10 minutes. Finally, participants filled in health and psychological questionnaires and were debriefed. The total length of the experiment procedure was approximately 3 to 4.5 hours. Participants received 25.- CHF/h for participation.

Supplementary III: blood DNA samples isolation for methylation analysis

Microarray-based DNA methylation analysis was performed at ServiceXS (ServiceXS B.V., Leiden, The Netherlands) on the HumanMethylation450 BeadChip (Illumina, Inc., San Diego, CA, U.S.A). All samples were randomized and processed in 6 plates. Plates were processed in 2 batches, with 2 and 4 plates respectively. In brief, the bisulfite conversion was performed with 500 ng genomic DNA input using the EZ DNA Methylation Gold Kit (Zymo Research, Irvine, CA USA). A bisulfite conversion quality control on the samples was performed with DNA qPCR reaction and subsequent melting curve analysis (Kristensen, Mikeska, Krypuy, & Dobrovic, 2008). The bisulfite-converted DNA was processed and hybridized to the HumanMethylation450 BeadChip (Illumina, Inc.), according to the manufacturer's instructions. The BeadChip images were scanned on the iScan system.

The data were extracted and analysed from the generated idat files using R (version: 12.15.2, R Development Core Team 2012) package RnBeads, (version: 0.99.9; (Yassen et al., 2013)). In brief, during preprocessing, the background was substracted using the methylumi package (method „noob"; (Davis, Du, Bilke, Tim, & Bootwalla, 2013)). The different probes signal intensity values were normalized using the probe type correction using subset-quantile within array normalization (Maksimovic, Gordon, & Oshlack, 2012). The following probe categories were excluded from the final dataset: non-CpG context probes, probes that overlap with more that 2 SNPs (used SNP frequency threshold was 0.01), probes associated to sex chromosomes and non-specific probes. Additionally, Greedycut algorithm iteratively removed the dataset probes and samples of the highest impurity (ß values with detection *p*-value below set threshold of 0.05 were considered as unreliable). Upon all filtering procedures, preprocessed dataset

consisted out of 567 samples and 449895 reliable probes. Sample crosscheck was done using the sex-prediction from the methylation data, as well as matching of rs probes from the Illumina 450k array and genotype calls from Affymetrix SNP 6.0 and imputed data.

Preprocessed data set was further processed in order to correct for possible bias sources. First the M values were calculated (M = log2(intensity m + 1/intensity u + 1), logit-transformation) since this value has been shown to be more valid for statistical analyses (Du et al., 2010). Next, data were scaled (z-transformation) for the 6 processing plates separately in order to minimize the effect of batch and technical bias. Additionally the dataset was corrected based on the result of the Principle Component Analysis (PCA). The correction was performed for the first 8 PCA residues, which were mainly associated with technical (plate, batch and sentrix position) and sampling (blood cell count) properties that could potentially be source of confounding bias in the dataset. In a last step, we regressed out sex and age.

Supplementary IV: Imaging methods

1. Data acquisition and analysis

Diffusion volumes were acquired using a single-shot echo-planar sequence, and consisted of 64 diffusion-weighted volumes (b=900 s/mm2) and one unweighted volume (b=0). Acquisition parameters were as following: TR=9000 ms, TE=82 ms, FOV=320 mm, GRAPPA R=2.0, voxel size 2.5x2.5x2.5 mm3. In total, 346 subjects of the imaging sample had diffusion-weighted data.

Diffusion data were analyzed using FSL v5.0.2 (http://www.fmrib.ox.ac.uk/fsl). DWI volumes were first visually inspected to detect any corrupted directions, e.g. due to motion (Sharman et al., 2011). In subjects where more than 1 direction was affected, those corrupted volumes were removed before proceeding. Two subjects for which more than 5 directions were affected were excluded from the analysis. Diffusion volumes were then motion corrected using the b=0 volume as a reference, and eddy current corrected. After removal of non-brain tissue, a diffusion tensor (DT) model was fitted on a voxel-by-voxel basis. Maps of fractional anisotropy (FA) and mean diffusivity (MD) were obtained from the DT model for further analyses.

Voxelwise statistical analysis of FA and MD maps was carried out using the Tract-Based Spatial Statistics (TBSS) toolbox of FSL (Smith et al. 2006). FA volumes were first non-linearly warped to FSL's high-resolution FA template (FMRIB58_FA) in the MNI152

space using the non-linear registration tool FNIRT. Next, a mean FA volume was computed and thinned to generate a mean FA skeleton, representing the center of white matter bundles common to all subjects. The skeleton was thresholded at FA>0.2 in order to reduce partial volume effects between white matter and other tissue classes. Finally, perpendicular projection of local maximal FA values onto the skeleton was done for each subject, accounting for residual variations in alignment. The computed non-linear warp and skeleton projection were also applied to the MD volumes, to create skeletonized MD maps.

2. Quantification of the results

Labelling of the significant voxels was done according to the JHU white-matter tractography atlas (Hua et al., 2008; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004) provided with FSL. For each of the twenty major white matter tracts included in the atlas, a tract of interest was created by applying a threshold of 10% to the probability map. Percentage of significant skeleton voxels belonging to each tract of interest was computed with regard to the total number of skeleton voxels, or to the total number of skeleton voxels in the tract. Additionally, the ICBM-DTI-81 White Matter Parcellation Map (Mori et al., 2008) was used to further quantify the results. Percentages of significant skeleton voxels belonging to each of the white matter structure were computed as for the tracts of interest.

Supplementary V: Additional tables and figures

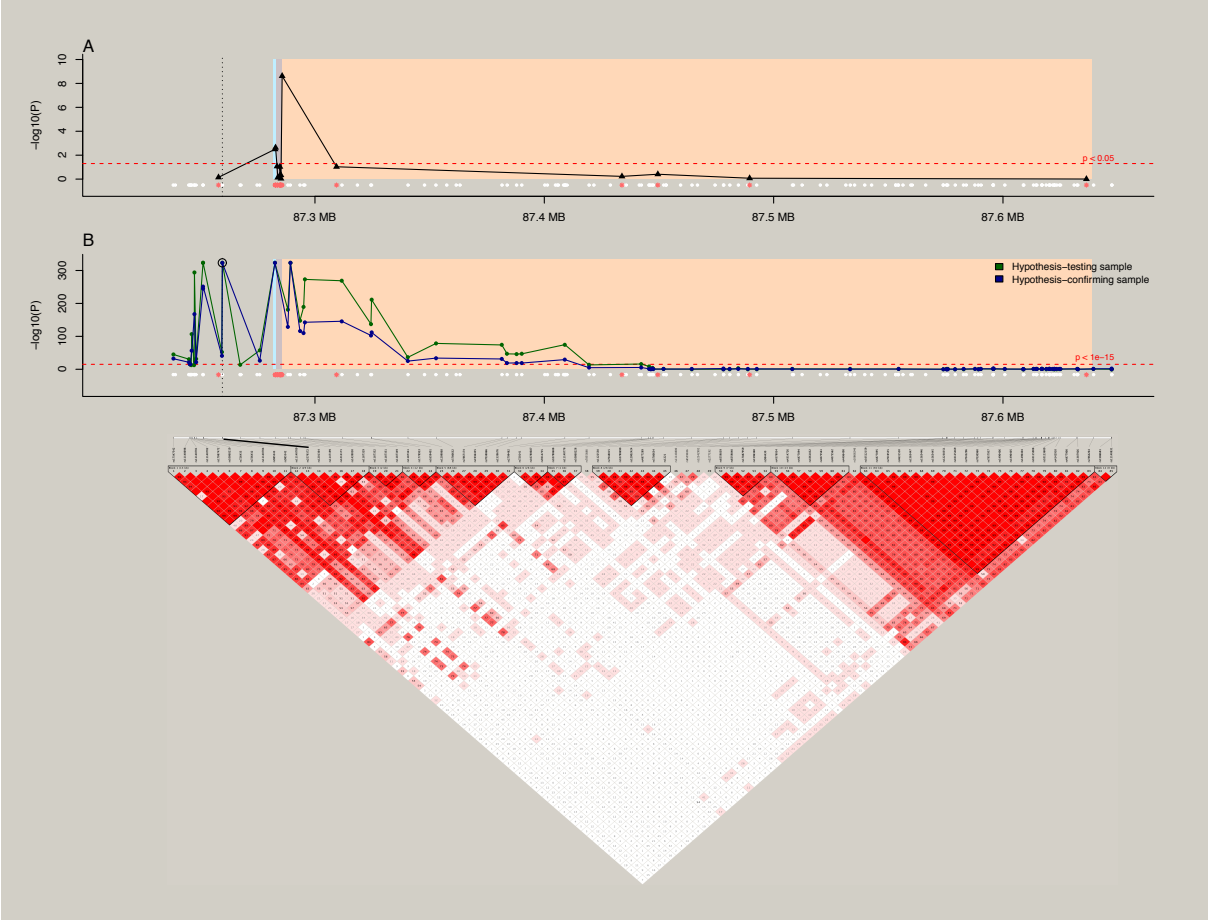

Figure S1: A) Association of SNP rs2579372 with 15 CpG-sites within NTRK2 gene. **B)** Association of SNP rs2579372 (recessive model) remaining 84 NTRK2 SNPs (recessive model) for the hypothesis-testing and –confirming sample separately. Bellow the LD structure of the 85 NTRK2 gene SNPs based on the hypothesis-testing sample is depicted. The position of the SNP rs2579372 is emphasized.

Table S1: Overview subjects per sample

Variables	Samples	
	sample 1	sample 2
Sex (women/men)	791/380	421/286
Age (mean ± SD)	23.01 ± 3.56	22.89 ± 3.24
Total number of subjects	1171	707

Table S2: SNP's passing Westfall-Young correction for SNP's and phenotypes (PT). All SNP's showed significant association specifically with mean positive arousal rating.

SNP	mean arousal rating	Model	p nominal	WY[1] (SNP+PT)	major/minor allele	homozygous major allele carriers			heterozygous carriers			homozygous minor allele carriers		
						N	MEAN	SD[2]	N	MEAN	SD[2]	N	MEAN	SD[2]
rs1187329	positive	Carrier-C	0.0004	0.07	C/T	353	0.02	1.06	556	0.09	0.95	260	-0.18	0.95
	negative		0.13	1.00			0.02	1.04		0.05	0.95		-0.06	0.98
	neutral		0.30	1.00			-0.01	1.00		0.02	1.01		-0.07	0.98
rs1187349	positive	Carrier-C	0.0003	0.05	C/T	345	0.05	1.06	573	0.07	0.95	251	-0.19	0.95
	negative		0.28	1.00			0.05	1.04		0.03	0.95		-0.04	0.99
	neutral		0.45	1.00			0.02	1.02		-0.01	1.00		-0.05	0.98
rs1212171	positive	Carrier-A	0.0003	0.04	A/G	356	0.02	1.05	554	0.09	0.95	261	-0.19	0.95
	negative		0.11	1.00			0.02	1.03		0.06	0.95		-0.07	0.98
	neutral		0.26	1.00			-0.01	1.00		0.02	1.01		-0.07	0.98
rs2579372	positive	Carrier-T	0.0003	0.05	T/C	348	0.03	1.05	545	0.09	0.95	268	-0.18	0.95
	negative		0.07	0.999			0.01	1.02		0.07	0.95		-0.07	0.98
	neutral		0.22	1.00			-0.02	0.99		0.04	1.02		-0.07	0.98
rs985542	positive	Carrier-G	8.49E-05	0.01	G/C	330	-0.01	1.05	568	0.11	0.96	270	-0.2	0.94
	negative		0.11	1.00			0.02	1.04		0.06	0.95		-0.06	0.96
	neutral		0.26	1.00			-0.03	1.00		0.03	1.02		-0.07	0.98
rs985543	positive	Carrier-T	0.0002	0.03	T/C	332	-0.0002	1.04	569	0.11	0.97	270	-0.19	0.93
	negative		0.16	1.00			0.02	1.04		0.05	0.95		-0.05	0.96
	neutral		0.32	1.00			-0.03	1		0.03	1.02		-0.06	0.98

[1]WY=Westfall Young for single nucleotide polymorphism (SNP) and phenotype (PT), [2]SD=standard deviation

Table S3: Association between methylation levels of 15 CpG-sites on NTRK2 gene and the two SNP's (rs2579372). One CpG-site survives the correction for multiple testing (see column *p* letters in italic).

CpG sites	BP	snp cpg p[1]	snp cpg r[2]	group[3]	snp cpg 50mer p[4]	snp cpg 50mer r[5]	Infinium Design Type[6]	Relation to UCSC CpG Island[7]	Replication blood to blood[8]	Replication blood saliva[9]	Mean beta[10]	Shapiro p logit[11]
cg14592798	87'257'941	0.714	-0.018	bad	0.532	-0.030	II		-0.105	-0.075	0.960	1.70E-06
cg13504245	87'282'610	0.003	0.143	medium	0.002	0.147	II	N_Shore	0.160	0.180	0.106	1.10E-06
cg22402007	87'282'823	0.002	0.147	good	0.002	0.147	II	N_Shore	0.688	0.622	0.229	1.20E-05
cg01009697	87'283'470	0.085	0.084	medium	0.085	0.084	II	Island	0.062	-0.227	0.050	6.30E-21
cg09539438	87'283'789	0.741	0.016	medium	0.741	0.016	II	Island	0.100	0.123	0.049	0.23
cg13965062	87'284'706	0.488	-0.034	bad	0.482	-0.034	I	Island	-0.136	-0.311	0.241	0.00037
cg13723118	87'284'722	0.092	0.082	medium	0.079	0.085	I	Island	0.236	-0.136	0.082	0.12
cg03628748	87285133	0.459	0.036	medium	0.459	0.036	II	Island	0.184	0.315	0.147	2.20E-05
cg08470639	87285186	0.904	0.006	medium	0.904	0.006	II	Island	0.227	0.172	0.119	6.00E-06
cg09926027	87285693	2.39E-09	0.284	medium	2.39E-09	0.284	II	Island	0.394	0.219	0.121	0.023
cg13698224	87'309'394	0.093	0.082	bad	0.093	0.082	II		-0.047	0.177	0.917	0.00012
cg14447193	87433864	0.592	0.026	good	0.592	0.026	II		0.652	0.460	0.918	0.49
cg14273545	87'449'508	0.391	-0.042	medium	0.397	-0.041	II		0.109	-0.135	0.941	0.12
cg13620631	87489528	0.844	-0.010	good	0.844	-0.010	II		0.689	0.554	0.205	0.0013
cg13654445	87636383	0.986	-0.001	medium	0.986	-0.001	II		0.014	0.169	0.965	3.70E-07

Legend:
[1] = *p* value for the association between SNP and CpGs
[2] = correlation between SNP and CpGs
[3] = quality classification
[4] = *p* value for the association between SNP and CpGs corrected for 50mer region
[5] = correlation between SNP and CpGs corrected for 50mer region
[6] = analysis plate
[7] = location of CpG site in UCSC annotation
[8] = quality control measure: replication in blood to blood
[9] = quality control measure: replication in salvia to blood
[10] = mean methylation level for each CpG site (values correspond to percentage values: 0=0%, 0.5= 50%, 1=100%)
[11] = *p* value for test of normality distribution

References

Bellenguez, C., Strange, A., Freeman, C., Donnelly, P., & Spencer, C. C. A. (2012). A robust clustering algorithm for identifying problematic samples in genome-wide association studies. *Bioinformatics (Oxford, England)*, *28*(1), 134-5. doi:10.1093/bioinformatics/btr599

Davis, S., Du, P., Bilke, S., Tim, T., & Bootwalla, M. (2013). Methylumi: handle Illumina methylation data. Retrieved from http:

Du, P., Zhang, X., Huang, C.-C., Jafari, N., Kibbe, W. A., Hou, L., & Lin, S. M. (2010). Comparison of Beta-value and M-value methods for quantifying methylation levels by microarray analysis. *BMC bioinformatics*, *11*, 587. doi:10.1186/1471-2105-11-587

Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., Calabresi, P. A., et al. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *NeuroImage*, *39*(1), 336-47. doi:10.1016/j.neuroimage.2007.07.053

Kristensen, L. S., Mikeska, T., Krypuy, M., & Dobrovic, A. (2008). Sensitive Melting Analysis after Real Time- Methylation Specific PCR (SMART-MSP): high-throughput and probe-free quantitative DNA methylation detection. *Nucleic acids research*, *36*(7), e42. doi:10.1093/nar/gkn113

Lang, P. J., Öhmann, A., & Vaitl, D. (1988). *The International Affective Picture System (slides).* Gainesville, FL.

Maksimovic, J., Gordon, L., & Oshlack, A. (2012). SWAN: Subset-quantile within array normalization for illumina infinium HumanMethylation450 BeadChips. *Genome biology*, *13*(6), R44. doi:10.1186/gb-2012-13-6-r44

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., et al. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage*, *40*(2), 570-82. doi:10.1016/j.neuroimage.2007.12.035

Sharman, M. A., Cohen-Adad, J., Descoteaux, M., Messé, A., Benali, H., & Lehericy, S. (2011). Impact of outliers on diffusion tensor and Q-ball imaging: clinical implications and correction strategies. *Journal of magnetic resonance imaging : JMRI*, *33*(6), 1491-502. doi:10.1002/jmri.22577

Wakana, S., Jiang, H., Nagae-Poetscher, L. M., van Zijl, P. C. M., & Mori, S. (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology*, *230*(1), 77-87. doi:10.1148/radiol.2301021640

Yassen, A., Müller, F., Lutsik, P., Walter, J., Lengauer, T., & Bock, C. (2013). Compehensive Analysis of DNA Methylation Data with RnBeads. Retrieved from

4.4. PKCA IS GENETICALLY LINKED TO MEMORY CAPACITY IN HEALTHY SUBJECTS AND TO RISK FOR POSTTRAUMATIC STRESS DISORDER IN GENOCIDE SURVIVORS

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PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors

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Strong memory of a traumatic event is thought to contribute to the development and symptoms of posttraumatic stress disorder (PTSD). Therefore, a genetic predisposition to build strong memories could lead to increased risk for PTSD after a traumatic event. Here we show that genetic variability of the gene encoding PKCα (*PRKCA*) was associated with memory capacity—including aversive memory—in nontraumatized subjects of European descent. This finding was replicated in an independent sample of nontraumatized subjects, who additionally underwent functional magnetic resonance imaging (fMRI). fMRI analysis revealed *PRKCA* genotype-dependent brain activation differences during successful encoding of aversive information. Further, the identified genetic variant was also related to traumatic memory and to the risk for PTSD in heavily traumatized survivors of the Rwandan genocide. Our results indicate a role for PKCα in memory and suggest a genetic link between memory and the risk for PTSD.

emotion | trauma | single nucleotide polymorphism

Emotional experiences are typically well remembered, but there is a large, partly genetically controlled, variability for this phenomenon (1). On the one hand, enhanced memory for emotionally arousing events can be seen as an adaptive mechanism, which helps us to remember important information (2). On the other hand, strong memory of an extremely aversive event may contribute to the development and symptoms of posttraumatic stress disorder (PTSD) (3–6). In a previous study we reported that a deletion variant of the *ADRA2B* gene was significantly associated with emotional memory in healthy humans and with traumatic memory in a traumatized population, but not significantly with the risk for PTSD (1). Thus, so far, there is no evidence indicating that genetic factors that predispose individuals to build strong aversive memories could also be risk factors for PTSD.

Considerable evidence suggests that protein kinases, in particular protein kinase A (PKA), protein kinase C (PKC), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and mitogen-activated protein kinase (MAPK), play an important role in the formation of emotional memory in animals (7, 8). To study whether the genes encoding these protein kinases are also related with human emotional memory, we applied a behavioral genetics approach and captured the variability of these genes with 2,005 single-nucleotide polymorphisms (SNPs) (*Methods* and *SI Appendix*).

The 2,005 selected SNPs were analyzed in an initial sample of 723 young healthy Swiss adults (476 females, 247 males; median age, 22 y; range, 18–35 y), who underwent memory testing. Subjects were presented 24 neutral, 24 positive, and 24 negative photographs in a random order. The photographs were taken from the international affective picture system (IAPS) (9) and presented for 2.5 s each. Immediately following the presentation of each photograph, subjects were asked to rate it for valence and arousal using the IAPS rating scales. After a delay of 10 min, during which subjects performed an *n*-back working memory task, subjects underwent a surprise free recall test of the previously presented pictures. Because we were interested in the link between aversive memory and PTSD, our target phenotype for the genetic association study was the number of freely recalled negative (aversive) pictures.

Results

Hypothesis Testing and Replication Sample. The analysis including all 2,005 SNPs revealed that SNP rs4790904, which is located within *PRKCA* (encoding protein kinase Cα), was significantly associated with memory for negative pictures after Bonferroni correction for multiple comparisons ($P_{\text{uncorrected}} = 0.000002$, $P_{\text{corrected}} = 0.004$; Table 1 and Table S1). There were no further Bonferroni-corrected significant SNPs. SNP rs4790904 was also significantly associated with memory for positive and neutral pictures (Table 1). Sex did not influence the association of rs4790904 with negative memory (sex × SNP interaction $P = 0.5$). This SNP was not associated with valence or arousal ratings of the pictures ($P \geq 0.8$; Table S2), indicating that the genotype-dependent differences in memory for negative pictures were not due to genotype-dependent differences in emotional arousal. Furthermore, rs4790904 was not associated with attention or working memory performance ($P \geq 0.6$; Table S3). In addition to the findings on

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Table 1. Genotype-dependent memory performance in the hypothesis-testing sample (n = 723)

Genotype, rs4790904	Negative pictures, mean ± SEM	Positive pictures, mean ± SEM	Neutral pictures, mean ± SEM	All pictures, mean ± SEM
AA, n = 459	11.1 ± 0.1	11.7 ± 0.1	6.9 ± 0.1	29.7 ± 0.4
AG, n = 232	10.0 ± 0.2	11.1 ± 0.2	6.0 ± 0.2	27.1 ± 0.5
GG, n = 32	9.3 ± 0.5	10.2 ± 0.5	5.8 ± 0.4	25.3 ± 1.2
	P = 0.000002	P = 0.006	P = 0.0004	P = 0.00001

short-term memory, analysis of data on free recall 24 h after picture presentation (available in the hypothesis-testing sample only) also revealed significant genotype-dependent differences in memory performance (Table S4).

SNP rs4790904 was further investigated in an independent sample of 394 healthy Swiss subjects, who performed the same tasks in a brain scanner (*Methods*). In this population, we could replicate the association of rs4790904 with memory for negative information (P = 0.028; Table 2). SNP rs4790904 was also significantly associated with memory for positive pictures (P = 0.005; Table 2), whereas the association with memory for neutral pictures was not significant (P = 0.284; Table 2). The direction of effect and the genetic model used (i.e., additive) were the same as in the initial discovery sample.

Functional Brain Imaging. In the next step, we used fMRI to identify genotype-independent and genotype-dependent differences in brain activity related to aversive memory in this population of 394 healthy subjects. The event-related fMRI design allowed us to investigate brain regions involved in memory formation by analyzing differential activity during encoding of subsequently remembered vs. subsequently forgotten events (subsequent memory analysis). Independently of genotype, this analysis revealed activation of a large network of neocortical and limbic brain regions, including the frontal, temporal, parietal, and occipital cortex; amygdala; hippocampus; insular cortex; and anterior cingulum (Fig. S1). These results are largely consistent with the findings of a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies of successful emotional memory encoding (10). *PRKCA* rs4790904 genotype-dependent, subsequent memory analyses for negative information revealed significant [$P < 0.05$, false discovery rate (FDR) corrected for whole brain] gene dose-dependent (with increasing number of A alleles) activity increases in the lateral and medial prefrontal cortex (Table 3 and Fig. 1). An additional region of interest (ROI) analysis for the amygdala and the hippocampus did not reveal significant (small-volume FDR corrected for the corresponding ROI) genotype-dependent activation differences in these brain regions. There were no significant activity increases with increasing number of G alleles. Thus, the present fMRI experiment revealed that the A allele, which was associated with increased memory for negative information, was also robustly related to increased brain activity in the lateral and medial prefrontal cortex during successful memory encoding of negative pictures. Previous studies have shown that these brain regions belong to a network involved in emotional memory encoding (10–12). Subsequent memory analyses for positive and neutral information did not reveal any significant genotype-dependent activation differences (at the same significance threshold as used for negative information, i.e., $P < 0.05$, FDR corrected for whole brain). This finding indicates that at the level of brain activation, significant PKCα genotype-dependent differences were observed only for negative information.

Because we used two different scanners in the fMRI study (*Methods*), we reanalyzed the data including scanner type as a covariate. This analysis revealed similar results to those described above.

Genetic Study in Traumatized Survivors of the Rwandan Genocide. We hypothesized that the *PRKCA* polymorphism, which predisposes individuals to build strong emotional memory, may also predispose to build strong traumatic memories after an aversive event and, possibly, also increase the risk for PTSD. We tested this hypothesis in 347 refugees who have fled from the Rwandan civil war and have been living in the Nakivale refugee camp in Uganda during the time of investigation (184 females, 163 males; median age, 34 y; range, 17–68 y). All subjects had experienced highly aversive situations and were examined by trained experts with a structured interview based on the Posttraumatic Diagnostic Scale (13) with the help of trained interviewers chosen from the refugee community. Traumatic events were assessed using a checklist of 36 war- and non-war–related traumatic event types (e.g., injury by a weapon, rape, accidents). The population consisted of 134 subjects fulfilling the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (5) for current PTSD and 213 subjects without current PTSD. *PRKCA* SNP rs4790904 was significantly associated with symptoms of reexperiencing the traumatic event (traumatic memory) with the same direction of effect as with memory for negative information in the healthy population (P = 0.033; Table 4). Furthermore, the A allele of rs4790904 was associated with increased avoidance symptoms (P = 0.037; Table 4) and with increased risk for PTSD (P = 0.009; Table 5). Sex did not influence the genotype effect on traumatic memory or PTSD risk (sex × SNP interaction $P \geq 0.7$). SNP rs4790904 was not associated with hyperarousal symptoms or with the number of experienced event types ($P > 0.5$). Of note, the A allele, which was the major allele in the Swiss population, was the rare allele in the Rwandese population. Such differences in allele and genotype frequency are commonly observed between genetically distinct populations. In the case of the present study, no conclusions can be drawn with regard to any possible functional relevance of this difference.

Table 2. Genotype-dependent memory performance in the replication sample (n = 394)

Genotype, rs4790904	Negative pictures, mean ± SEM	Positive pictures, mean ± SEM	Neutral pictures, mean ± SEM	All pictures, mean ± SEM
AA, n = 234	11.3 ± 0.2	12.3 ± 0.2	6.9 ± 0.2	30.5 ± 0.5
AG, n = 139	10.7 ± 0.3	11.6 ± 0.3	6.5 ± 0.2	28.7 ± 0.7
GG, n = 21	10.1 ± 0.6	10.6 ± 0.6	6.5 ± 0.7	27.1 ± 1.5
	P = 0.028	P = 0.005	P = 0.284	P = 0.014

Table 3. *PRKCA* rs4790904 genotype-dependent, subsequent memory analysis for negative information (gene dose-dependent activity increases with increasing number of *A* alleles)

Region	BA	No. voxels	L/R	MNI coordinates			*T*
				x	*y*	*z*	
Middle frontal gyrus	6	51	L	−33	3	40	4.56*
Middle frontal gyrus	9	47	L	−47	25	36	4.45*
Inferior frontal gyrus	46/47	41	L	−44	38	0	4.24*
Superior frontal gyrus	8	36	L	−6	33	52	3.83*

BA, Brodmann area; L/R, left/right hemisphere.
*Thresholded at $P < 0.05$, FDR corrected for whole brain.

Discussion

The present results indicate that PKCα is genetically linked to memory capacity (including aversive memory) in nontraumatized individuals and to traumatic memory and the risk for PTSD in heavily traumatized genocide survivors. Unlike the previously reported *ADRA2B* deletion variant (1), PKCα seems to be related to memory independent of emotional valence, because the genetic association in healthy individuals was not consistently restricted to emotional information.

Free recall of pictures in healthy subjects as assessed in the present study involves voluntary retrieval of image-based memory. Encoding of this memory depends on a large network of neocortical and limbic brain regions, including the frontal, temporal, parietal, and occipital cortex; amygdala (especially for emotionally arousing information); hippocampus; insular cortex; and anterior cingulum (10). In PTSD, intrusive reexperiencing of the traumatic event consists of a primarily involuntary activation of representations (emotional memories) that contain detailed sensory and perceptual images. At the same time, it has been proposed that due to a reduced hippocampal involvement, these emotional memories are not well contextualized (14) (for review see ref. 15). In the nontraumatized population the neuroimaging findings revealed that the *A* allele went along with more activation in prefrontal regions, but, interestingly, not with increased activation in medial temporal structures, such as the amygdala and hippocampus. There is compelling evidence that the amygdala plays an important role in enhancing the formation of memory for emotionally arousing information (11) and that the hippocampus is crucial for binding memory items to their context and for the successful transfer of this information into long-term memory (8, 16). It is important to note that because scanning in the present study was restricted to the encoding phase, we cannot exclude that genotype-dependent activation differences in medial temporal lobe regions may have occurred later in the memory formation process.

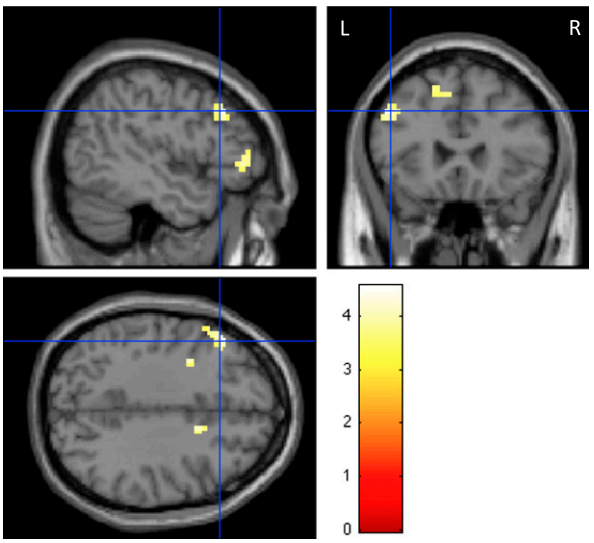

Fig. 1. *PRKCA* rs4790904 genotype-dependent differences in brain activity related to successful encoding of memory for negative information in 394 healthy young subjects. Displayed are gene dose-dependent (with increasing number of *A* alleles) increases in activity in the lateral and medial prefrontal cortex. The blue cross indicates the peak activation in the left dorsolateral prefrontal cortex at (−47 25 36). Activations are overlaid on sagittal (*Upper Left*), coronal (*Upper Right*), and axial sections of a T1-weighted magnetic resonance image of SPM5, displayed at a whole brain FDR-corrected threshold of $P < 0.05$ and using color-coded *t* values. L, left side of the brain; R, right side of the brain.

Table 4. Correlation of the *A* allele of rs4790904 with PTSD-related symptoms in the Rwanda sample

	Intrusions	Avoidance	Hyperarousal
Spearman ρ	0.115	0.112	0.030
Significance *P*	0.033	0.037	0.579
n	347	347	347

Although theoretical considerations might have implied that individuals who are prone to build strong emotional memories are at risk for developing PTSD after a traumatic experience, there is only weak empirical evidence supporting this assumption. Several studies have found increased implicit and explicit emotional memory functions in patients with PTSD (17–19), but also the opposite has been reported (20). It is important to note that data on memory performance acquired in patients with PTSD are difficult to interpret, because changes in mood, motivation, attention, or arousal can indirectly affect memory performance in both directions. Furthermore, even specific memory changes could be a consequence of the disease or preexisting risk factors. The same difficulty regarding interpretation exists for imaging data acquired in PTSD patients, because neuroanatomical or neurofunctional abnormalities may reflect an underlying causal factor or a consequence of the disorder. For example, it has been found that patients with PTSD have reduced hemodynamic responses in the medial prefrontal cortex (21), which fits with the idea that decreased prefrontal activity, through amygdala disinhibition, could lead to increased formation of traumatic memories and predispose to PTSD. However, another study found that encoding of later remembered negative words vs. baseline was associated with increased activations in the cingulate cortex and dorsomedial prefrontal cortex in complex PTSD compared with healthy controls (22). Moreover, a recent study has demonstrated that damage to the medial prefrontal cortex protects against PTSD (23). Also in the present study, we found that the *G* allele, which was related to decreased emotional memory and decreased prefrontal activity in healthy humans, was related to decreased risk for PTSD.

Considerable evidence indicates that PKC plays an important role in learning and memory (7). For example, it has been shown that PKC targets phosphorylation sites on the C-terminal

Table 5. Association between *PRKCA* SNP rs4790904 and risk for PTSD in the Rwanda sample

Genotype	No PTSD	PTSD	Total
GG	90, 42.3%	37, 27.6%	127, 36.6%
AG	99, 46.5%	76, 56.7%	175, 50.4%
AA	24, 11.2%	21, 15.7%	45, 13.0%
	$\chi^2 = 6.8$, df = 1, $P_{additive} = 0.009$		

domain of NR2B, which can modulate NMDAR conductance (24). PKCs include several isoforms and it has been shown that mice with a specific deletion of PKCβ have impaired fear conditioning when tested 24 h after training (25). Furthermore, it has been shown that the α1-adrenergic receptor pathway is capable of activating PKCα, which may represent a mechanism for enhancing memory (26). In our study, a *PRKCA* genotype-dependent difference was observed as early as 10 min after learning in the Swiss cohort of healthy young individuals, suggesting that short-term memory processes were already affected. The analysis of additional data on free recall 24 h after picture presentation, reflecting long-term memory performance in the Swiss cohort, also revealed significant genotype-dependent differences in memory performance. Furthermore, the genotype was also related to long-term traumatic memories in individuals who experienced life-threatening situations, suggesting a role of *PRKCA* in both short- and long-term memory processes.

In summary, the present results provide evidence for a role of *PRKCA* in memory, including aversive and traumatic memory. Our study also points to a genetic link between the predisposition to build strong memory and the risk for PTSD and indicates differential genetic risks for different clusters of PTSD symptoms. Genetic analyses may thus help to uncover PTSD dimensions with different symptom patterns, a subtyping that may be necessary to improve understanding and treatment of posttrauma psychopathology.

Methods

Emotional and Working Memory Testing. ***Picture task.*** Stimuli consisted of 72 pictures that were selected from the IAPS (9) as well as from in-house standardized picture sets that allowed us to equate the pictures for visual complexity and content (e.g., human presence). On the basis of normative valence scores (from 1 to 9), pictures were assigned to emotionally negative (2.3 ± 0.6), emotionally neutral (5.0 ± 0.3), and emotionally positive (7.6 ± 0.4) conditions, resulting in 24 pictures for each emotional valence. Four additional pictures showing neutral objects were used to control for primacy and recency effects in memory. Two of these pictures were presented in the beginning and two at the end of the picture task. They were not included in the analysis. In addition, 24 scramble pictures were used. The background of the scrambled pictures contained the color information of all pictures used in the experiment (except primacy and recency pictures), overlaid with a crystal and distortion filter (Adobe Photoshop CS3). In the foreground, a mostly transparent geometrical object (rectangle or ellipse of different sizes and orientations) was shown. Pictures were presented in the scanner using MR-compatible liquid crystal display goggles (Visuastim XGA; Resonance Technology). Eye correction was used when necessary.

The pictures were presented for 2.5 s in a quasi-randomized order so that at maximum four pictures of the same category occurred consecutively. A fixation cross appeared on the screen for 500 ms before each picture presentation. Trials were separated by a variable intertrial period of 9–12 s (jitter) that was equally distributed for each stimulus category. During the intertrial period, participants subjectively rated the picture showing scenes according to valence (negative, neutral, positive) and arousal (large, medium, small) on a three-point scale (self assessment manikin, SAM) by pressing a button with a finger of their dominant hand. Participants were not told that they had to remember the pictures for later recall.

Ten minutes after picture presentation, memory performance was tested using a free-recall task, which required participants to write down a short description (a few words) of the previously seen pictures. Remembered primacy and recency pictures as well as training pictures were excluded from the analysis. No time limit was set for this task. A picture was scored as correctly recalled if the rater could identify the presented picture on the basis of the subject's description. Two trained investigators independently rated the descriptions for recall success (interrater reliability >99%). A third independent rater decided on pictures, which were rated differently.

Subjects (from the hypothesis-testing sample) performed a similar free-recall test 24 h after picture presentation.

Working memory task. Between picture presentation and recall, participants performed on the 0- and 2-back versions of the *n*-back working memory task (27). In this task, letters are presented successively in the center of the screen. In the 0-back condition, subjects had to respond to the occurrence of the letter "x", which is a baseline measure of general attention, concentration, and reaction time. The 2-back task requires subjects to respond to a letter repetition with one intervening letter (g – S – f – s). The latter condition required both the maintenance of the last two letters in memory and updating of these remembered stimuli as each new stimulus was presented.

Subjects were free of any lifetime neurological or psychiatric illness and did not take any medication at the time of the experiment. The experiments were approved by the ethics committee of the Canton of Basel. Written informed consent was obtained from all subjects before participation.

fMRI Experiment. ***Participants.*** A total of 394 healthy young subjects (241 females, 153 males; median age, 22 y; range, 18–30 y; 234 *AA* genotype carriers of SNP rs4790904, 139 *AG* genotype carriers of SNP rs4790904, and 21 *GG* genotype carriers of SNP rs4790904) were included in the study. All subjects were right-handed, free of any lifetime neurological or psychiatric illness, and did not take any medication at the time of the experiment. The experiments were approved by the ethics committees of the Cantons of Zurich and Basel. Written informed consent was obtained from all subjects before participation. Subjects were scanned either in Zurich (n = 86) or in Basel (n = 308), using the identical design.

Emotional and working memory task. We used identical tasks to those described above.

Procedure. After receiving general information about the study and giving their informed consent, participants were instructed and then trained on the picture task they later performed in the scanner. After training, they were positioned in the scanner. The participants received earplugs and headphones to reduce scanner noise. Their heads were fixated in the coil using small cushions, and they were told not to move their heads. Functional MR images were acquired during the performance of the picture task in two separate sessions (total scanning time ~30 min). After finishing the tasks, participants left the scanner and were taken to a separate room for free recall of the pictures. Finally, participants filled out questionnaires, gave saliva for genotype analysis, and were debriefed. The total length of the experimental procedure was ~3 h. Participants received 25 Swiss francs/h for participation. Saliva samples were obtained from each person, using an Oragene DNA Self-Collection Kit (DNA Genothek). DNA was extracted from saliva using standard protocols.

fMRI data acquisition and processing. Zurich site. Measurements were performed on a Philips Intera 3 T whole-body MR unit equipped with an eight-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity encoded (28) single-shot echo-planar sequence (SENSE-sshEPI). We used the following acquisition parameters: echo time (TE) = 35 ms, field of view (FOV) = 22 cm, acquisition matrix = 80 × 80, interpolated to 128 × 128, voxel size = 2.75 × 2.75 × 4 mm^3, and SENSE acceleration factor R = 2.0. Using a midsaggital scout image, 32 contiguous axial slices were placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a repetition time (TR) = 3,000 ms (α = 82°). The first two acquisitions were discarded due to T1 saturation effects.

Basel site. Measurements were performed on a Siemens Magnetom Verio 3 T whole-body MR unit equipped with a 12-channel head coil. Functional time series were acquired with a single-shot echo-planar sequence using parallel imaging (GRAPPA). We used the following acquisition parameters: TE = 35 ms, FOV = 22 cm, acquisition matrix = 80 × 80, interpolated to 128 × 128, voxel size = 2.75 × 2.75 × 4 mm^3, and GRAPPA acceleration factor R = 2.0. Using a midsaggital scout image, 32 contiguous axial slices were placed along the AC–PC plane covering the entire brain with a TR = 3,000 ms (α = 82°). The first two acquisitions were discarded due to T1 saturation effects.

Preprocessing and data analysis were performed using SPM5 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom) implemented in MATLAB 2008a (MathWorks). Volumes were slice-time corrected to the first slice, realigned to the first acquired volume, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel. A 128-s cutoff high-pass filter was added to the confound partition of the design matrix to account for low-frequency drifts, and a correction for intrinsic autocorrelations was included in the analysis. For each subject, evoked hemodynamic responses to event types were modeled with a delta (stick) function corresponding to presentation of each stimulus category (negative, positive, neutral, and scrambled pictures, respectively) convolved with a canonical hemodynamic response function within the context of a general linear model (GLM). The pictures accounting for possible primacy and recency effects as well as button presses during valence and arousal ratings were modeled separately. In addition, six movement parameters from spatial realigning were included as regressors of no interest. The contrast between brain activity during encoding of pictures subsequently remembered and brain activity during encoding of pictures subsequently forgotten was calculated individually

using a fixed-effects model (first-level analysis). The resulting contrast parameters were then used for genotype-dependent analyses in a random-effects model (second-level analysis). Specifically, we used a regression model to analyze gene-dose–dependent differences in brain activity (with the number of *A* alleles as a covariate). We used a threshold of $P < 0.05$, FDR corrected for whole brain, and a minimum number of 30 adjacent voxels for an exploratory analysis of the whole brain. For the hippocampus and the amygdala, we additionally used the left and right amygdala and the left and right hippocampus as ROIs, where small volume correction was applied with a threshold of $P < 0.05$ (FDR corrected). The hippocampus and amygdala ROIs were defined by the Talairach atlas with the categorization in Brodmann areas (29), implemented in the software WFU PickAtlas v2.4 (30).

Rwanda Sample. As the Nakivale refugee camp has grown over the last decade and is spread over a large area, participants were sampled proportionally to the population size from each zone. To exclude genetic relatives in the samples, only one person per household was interviewed. Interviewers had been trained to detect current alcohol abuse and acute psychotic symptoms; candidates exhibiting these signs were excluded. All subjects had experienced highly aversive traumatic situations and were examined in 2006/2007 by trained experts, using a structured interview based on the Posttraumatic Diagnostic Scale (PDS) (13) with the help of trained interpreters. Traumatic events were assessed with a checklist of 36 war- and non-war–related traumatic event types, e.g., injury by weapon, rape, accident (1, 31). Traumatic load was estimated by assessing the number of different traumatic event types experienced or witnessed. This measure is considered more reliable than assessing the frequency of traumatic events (31). Depressive symptoms were assessed with the depression section of the Hopkins Symptom Checklist (HSCL-D) (32). A subset of this sample has been analyzed in previous studies (1, 33). The procedures were approved by the Ethics Committees of the University of Konstanz and the Mbarara University of Science and Technology, Mbarara, Uganda.

The PDS and event list were completed in the form of a standardized interview. Interviewers were first trained in a 6-wk course on principles of quantitative data collection and interviewing techniques. Instruments were translated into Kinyarwanda, using several steps of translations, blind back-translations, and subsequent corrections by independent groups of translators (34). Following the translations, the psychometric properties of the translated scales were investigated in a validation study including a retest spanning a 2-wk period and a cross-validation with expert rating (35). To avoid known ceiling effects (36), subjects were selected to have experienced no more than 16 traumatic event types.

Saliva samples were obtained from each person, using an Oragene DNA Self-Collection Kit (DNA Genothek). DNA was extracted from saliva using standard protocols.

SNP Selection. To capture the variability of the genes encoding PKA, PKC, CaMKII, MAPK, and their subunits, 2,005 intragenic SNPs that are present on the Affymetrix Human SNP Array 6.0 were selected. In addition to the SNPs being intragenic, the following inclusion criteria for each SNP were set: minor allele frequency (MAF) $\geq$ 5%; nondeviance from Hardy–Weinberg equilibrium ($P_{Fisher} \geq 0.01$); and call rate $\geq$ 95%, i.e., a SNP was excluded if more than 5% of all individuals failed to have genotypic information for this SNP (*SI Appendix*).

Array-Based SNP Genotyping. Samples were processed as described in the Genome-Wide Human SNP Nsp/Sty 6.0 User Guide (Affymetrix). Briefly, genomic DNA concentration was determined by fluorometry (Qubit dsDNA BR Assay Kit; Invitrogen) in a Qubit 1.0 fluorometer and adjusted to 50 ng/μL in water. Two hundred fifty nanograms of DNA was digested in parallel with 10 units of StyI and NspI restriction enzymes (New England Biolabs) for 2 h at 37 °C. Enzyme-specific adaptor oligonucleotides were then ligated onto the digested ends with T4 DNA Ligase for 3 h at 16 °C. After adjustment to 100 μL with water, 10 μL of the diluted ligation reactions were subjected to PCR. Three PCR reactions of 100 μL were performed for Sty-digested products and four PCR reactions for Nsp. PCR was performed with Titanium Taq DNA Polymerase (Clontech) in the presence of 4.5 μM PCR primer 002 (Affymetrix), 350 μM each dNTP (Clontech), 1 M G-C Melt (Clontech), and 1× Titanium Taq PCR Buffer (Clontech). Cycling parameters were as follows: initial denaturation at 94 °C for 3 min; amplification at 94 °C for 30 s and 60 °C for 45 s and then extension at 68 °C for 15 s, repeated a total of 30 times; and final extension at 68 °C for 7 min. Reactions were then verified to migrate at an average size between 200 and 1,100 bp, using 2% Tris-borate-EDTA (TBE) gel electrophoresis [2 g agarose (Sigma A9539; Sigma-Aldrich) in 100 mL of 1× TBE buffer]. PCR products were combined and purified with the Filter Bottom Plate (Millipore; P/N MDRLN0410), using Agencourt AMPure XP Beads (Beckman Coulter). Purified PCR products were quantified on a Zenith 200rt microplate reader (Anthos-Labtec). Four to 5 μg/μL was obtained on average for each sample. From this stage on, the SNP Nsp/Sty 5.0/6.0 Assay Kit (Affymetrix) was used. Around 250 μg of purified PCR products were fragmented using 0.5 unit of DNase I at 37 °C for 35 min. Fragmentation of the products to an average size less than 180 bp was verified using 4% TBE gel electrophoresis. Following fragmentation, the DNA was end-labeled with 105 units of terminal deoxynucleotidyl transferase at 37 °C for 4 h. The labeled DNA was then hybridized onto the Genome-Wide Human SNP 6.0 Array at 50 °C for 18 h at 60 rpm (GeneChip Hybridization Oven 645, Affymetrix, Santa Clara, CA). The hybridized array was washed, stained, and scanned according to the manufacturer's (Affymetrix) instructions, using the Affymetrix GeneChip Command Console (AGCC, version 3.2.0.1515). Generation of SNP calls and Array quality control were performed using the command line programs of the Affymetrix Power Tools package (version apt-1.14). According to the manufacturer's recommendation, contrast quality control (QC) was chosen as QC metric, using the default value of greater than or equal to 0.4. Mean call rate for all samples averaged >98.5%. All samples passing QC criteria were subsequently genotyped using the Birdseed (v2) algorithm.

Statistical Analyses. All nongenetic statistical analyses were done with a standard software package (SPSS Statistics, version 19). Wherever appropriate, nonparametric methods (e.g., rank correlation) were used. The nominal significance threshold was set to $P \leq 0.05$. The corrected significance threshold (i.e., Bonferroni correction for the analysis of 2,005 SNPs) was set to $P < 0.000025$. Golden Helix SNP and Variation Suite 7 (SVS7, version 7.5.3) was used for statistical analysis of genetic data. Analyses were run under the assumption of an additive model. Population stratification was assessed with EIGENSTRAT (37) by analyzing all genome-wide, array-based autosomal SNPs passing QC criteria. Principal component analysis (PCA) was first applied to reduce genetic variation to a few dimensions. For PCA, default parameters were used (i.e., definition of 10 principal components in five iterations; outlier criterion was 6 SDs). We also applied the Genomic Control program that is implemented in the EIGENSTRAT package to compute the inflation factor λ (38).

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1. de Quervain DJ, et al. (2007) A deletion variant of the alpha2b-adrenoceptor is related to emotional memory in Europeans and Africans. *Nat Neurosci* 10:1137–1139.
2. McGaugh JL (2003) *The Making of Lasting Memory. Memory and Emotion* (Weidenfeld and Nicolson, London).
3. Phelps EA, LeDoux JE (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48:175–187.
4. Pitman RK (1989) Post-traumatic stress disorder, hormones, and memory. *Biol Psychiatry* 26:221–223.
5. American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (American Psychiatric Association, Washington, DC), 4th Ed.
6. Brewin CR, Holmes EA (2003) Psychological theories of posttraumatic stress disorder. *Clin Psychol Rev* 23:339–376.
7. Rodrigues SM, Schafe GE, LeDoux JE (2004) Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. *Neuron* 44:75–91.
8. McGaugh JL (2000) Memory—a century of consolidation. *Science* 287:248–251.
9. Lang P, Bradley M, Cuthbert B (1999) *International Affective Picture System (IAPS): Instruction Manual and Affective Ratings*, Technical Report A-4, The Center for Research in Psychophysiology (University of Florida, Gainesville, FL).
10. Murty VP, Ritchey M, Adcock RA, LaBar KS (2010) fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia* 48:3459–3469.
11. McGaugh JL (2002) Memory consolidation and the amygdala: A systems perspective. *Trends Neurosci* 25:456–461.
12. Todd RM, Palombo DJ, Levine B, Anderson AK (2011) Genetic differences in emotionally enhanced memory. *Neuropsychologia* 49:734–744.
13. Foa EB, Cashman L, Jaycox L, Perry K (1997) The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. *Psychol Assess* 9:445–451.
14. Elbert T, Schauer M (2002) Burnt into memory. *Nature* 419:883.
15. Brewin CR, Gregory JD, Lipton M, Burgess N (2010) Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychol Rev* 117:210–232.

16. Ranganath C (2010) A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus* 20:1263–1290.
17. Paunovi N, Lundh LG, Ost LG (2002) Attentional and memory bias for emotional information in crime victims with acute posttraumatic stress disorder (PTSD). *J Anxiety Disord* 16:675–692.
18. Moradi AR, Taghavi R, Neshat-Doost HT, Yule W, Dalgleish T (2000) Memory bias for emotional information in children and adolescents with posttraumatic stress disorder: A preliminary study. *J Anxiety Disord* 14:521–534.
19. Michael T, Ehlers A, Halligan SL (2005) Enhanced priming for trauma-related material in posttraumatic stress disorder. *Emotion* 5:103–112.
20. Bremner JD, et al. (2003) Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol Psychiatry* 53:879–889.
21. Bremner JD, et al. (1999) Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry* 156: 1787–1795.
22. Thomaes K, et al. (2011) Increased anterior cingulate cortex and hippocampus activation in complex PTSD during encoding of negative words. *Soc Cogn Affect Neurosci*.
23. Koenigs M, et al. (2008) Focal brain damage protects against post-traumatic stress disorder in combat veterans. *Nat Neurosci* 11:232–237.
24. Liao GY, Wagner DA, Hsu MH, Leonard JP (2001) Evidence for direct protein kinase-C mediated modulation of N-methyl-D-aspartate receptor current. *Mol Pharmacol* 59: 960–964.
25. Weeber EJ, et al. (2000) A role for the beta isoform of protein kinase C in fear conditioning. *J Neurosci* 20:5906–5914.
26. Dong C, Godwin DW, Brennan PA, Hegde AN (2009) Protein kinase Calpha mediates a novel form of plasticity in the accessory olfactory bulb. *Neuroscience* 163:811–824.
27. Gevins A, Cutillo B (1993) Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr Clin Neurophysiol* 87:128–143.
28. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P (1999) SENSE: sensitivity encoding for fast MRI. *Magn Reson Med* 42:952–962.
29. Lancaster JL, et al. (2000) Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 10:120–131.
30. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19:1233–1239.
31. Neuner F, et al. (2004) Psychological trauma and evidence for enhanced vulnerability for posttraumatic stress disorder through previous trauma among West Nile refugees. *BMC Psychiatry* 4:34–41.
32. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L (1974) The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behav Sci* 19:1–15.
33. Kolassa IT, et al. (2010) Association study of trauma load and SLC6A4 promoter polymorphism in posttraumatic stress disorder: Evidence from survivors of the Rwandan genocide. *J Clin Psychiatry* 71:543–547.
34. Onyut LP, et al. (2004) The Nakivale Camp Mental Health Project: Building local competency for psychological assistance to traumatised refugees. *Intervention (Amstelveen)* 2:90–107.
35. Neuner F, et al. (2008) Treatment of posttraumatic stress disorder by trained lay counselors in an African refugee settlement: A randomized controlled trial. *J Consult Clin Psychol* 76:686–694.
36. Kolassa IT, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJ (2010) The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-o-methyltransferase Val(158)Met polymorphism. *Biol Psychiatry* 67:304–308.
37. Price AL, et al. (2006) Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38:904–909.
38. Devlin B, Roeder K (1999) Genomic control for association studies. *Biometrics* 55: 997–1004.

Marker	Chromosome	Position	dbSNP RS ID	Associated Gene	Cytoband	Minor Allele Freq.	HWE P
SNP_A-8403040	1	2013924	rs2459994	PRKCZ	p36.33	0.209	0.089
SNP_A-1908463	1	2017761	rs7513222	PRKCZ	p36.33	0.346	0.876
SNP_A-8654028	1	2023116	rs908742	PRKCZ	p36.33	0.347	0.680
SNP_A-8581056	1	2030758	rs4648807	PRKCZ	p36.33	0.413	0.337
SNP_A-1955996	1	2037444	rs3107146	PRKCZ	p36.33	0.122	0.295
SNP_A-2131370	1	2051829	rs3107157	PRKCZ	p36.33	0.418	0.635
SNP_A-2203009	1	2059541	rs3753242	PRKCZ	p36.33	0.071	0.080
SNP_A-8631231	1	2061598	rs3128298	PRKCZ	p36.33	0.088	0.793
SNP_A-8351773	1	2063964	rs12026349	PRKCZ	p36.33	0.104	0.309
SNP_A-8438441	1	2064928	rs451061	PRKCZ	p36.33	0.387	0.429
SNP_A-2098546	1	2067269	rs385039	PRKCZ	p36.33	0.284	0.868
SNP_A-8385581	1	2071502	rs3107126	PRKCZ	p36.33	0.105	0.175
SNP_A-8404055	1	2072349	rs262669	PRKCZ	p36.33	0.388	0.295
SNP_A-8317896	1	2072426	rs2257182	PRKCZ	p36.33	0.398	0.069
SNP_A-2264565	1	2094841	rs262641	PRKCZ	p36.33	0.282	0.418
SNP_A-1788728	1	2095738	rs3128309	PRKCZ	p36.33	0.099	0.668
SNP_A-4250389	1	2100120	rs626479	PRKCZ	p36.33	0.281	0.801
SNP_A-8710152	1	27556983	rs4970520	MAP3K6	p36.11	0.210	0.397
SNP_A-8676195	1	27562884	rs4075731	MAP3K6	p36.11	0.361	0.413
SNP_A-8379006	1	56895055	rs2143749	PRKAA2	p32.2	0.354	0.778
SNP_A-1946127	1	56899238	rs2746349	PRKAA2	p32.2	0.499	0.520
SNP_A-1900762	1	56899463	rs2796529	PRKAA2	p32.2	0.147	0.138
SNP_A-2130663	1	56899507	rs2746347	PRKAA2	p32.2	0.124	0.345
SNP_A-8418742	1	56900427	rs2796528	PRKAA2	p32.2	0.173	0.122
SNP_A-4202067	1	56903176	rs2796519	PRKAA2	p32.2	0.472	0.964
SNP_A-1832915	1	56905582	rs10889008	PRKAA2	p32.2	0.451	0.840
SNP_A-8409936	1	56911958	rs2746339	PRKAA2	p32.2	0.469	0.192
SNP_A-8438724	1	56917661	rs2092595	PRKAA2	p32.2	0.470	0.156
SNP_A-2000072	1	56922085	rs2796512	PRKAA2	p32.2	0.475	0.161
SNP_A-1960148	1	56925602	rs7515414	PRKAA2	p32.2	0.443	0.654
SNP_A-8345751	1	56930881	rs7419053	PRKAA2	p32.2	0.442	0.891
SNP_A-8347257	1	56950377	rs857147	PRKAA2	p32.2	0.482	0.074
SNP_A-2222110	1	84323437	rs6701486	PRKACB	p31.1	0.227	0.063
SNP_A-8515179	1	84325194	rs7546625	PRKACB	p31.1	0.162	0.246
SNP_A-8411322	1	84328496	rs6703653	PRKACB	p31.1	0.311	0.187
SNP_A-2102459	1	84329111	rs12405120	PRKACB	p31.1	0.452	0.587
SNP_A-4301860	1	84334853	rs10493750	PRKACB	p31.1	0.457	0.614
SNP_A-2000160	1	84343593	rs2642186	PRKACB	p31.1	0.223	0.052
SNP_A-8527233	1	84357711	rs12724598	PRKACB	p31.1	0.237	0.907
SNP_A-1920852	1	84362717	rs1016379	PRKACB	p31.1	0.232	0.537
SNP_A-2028586	1	84362903	rs12723299	PRKACB	p31.1	0.460	0.063
SNP_A-1789609	1	84363115	rs2139931	PRKACB	p31.1	0.232	0.537
SNP_A-1932323	1	84366987	rs11163905	PRKACB	p31.1	0.460	0.124
SNP_A-8301655	1	84376075	rs2642183	PRKACB	p31.1	0.235	0.494
SNP_A-8536993	1	84377525	rs6576962	PRKACB	p31.1	0.462	0.141
SNP_A-8672434	1	84396892	rs6696125	PRKACB	p31.1	0.452	0.054
SNP_A-8498602	1	84401243	rs12129768	PRKACB	p31.1	0.109	0.252
SNP_A-2289186	1	84421173	rs589373	PRKACB	p31.1	0.111	0.872
SNP_A-4202513	1	84431717	rs6661411	PRKACB	p31.1	0.133	0.754
SNP_A-2094409	1	84435529	rs2134648	PRKACB	p31.1	0.455	0.052
SNP_A-8386970	1	84436778	rs12125649	PRKACB	p31.1	0.053	0.556
SNP_A-2021835	1	84440040	rs603939	PRKACB	p31.1	0.219	0.075
SNP_A-2293326	1	84450848	rs2134646	PRKACB	p31.1	0.450	0.211
SNP_A-2115979	1	145095103	rs11584787	PRKAB2	q21.1	0.262	0.869
SNP_A-8446640	1	145095366	rs1837984	PRKAB2	q21.1	0.425	0.326
SNP_A-1965870	1	145097540	rs2304893	PRKAB2	q21.1	0.075	0.775
SNP_A-8712903	1	145102761	rs6593738	PRKAB2	q21.1	0.425	0.958
SNP_A-1956171	1	145102789	rs6593739	PRKAB2	q21.1	0.384	0.798
SNP_A-8575061	1	145108310	rs3766522	PRKAB2	q21.1	0.247	0.893
SNP_A-2212982	1	204937958	rs4845129	MAPKAPK2	q32.1	0.237	0.768
SNP_A-8701207	1	204938407	rs10863784	MAPKAPK2	q32.1	0.108	0.659
SNP_A-8348404	1	204939110	rs4845130	MAPKAPK2	q32.1	0.227	0.113
SNP_A-4202986	1	204940357	rs17350838	MAPKAPK2	q32.1	0.202	0.842
SNP_A-4290223	1	204940780	rs17350845	MAPKAPK2	q32.1	0.235	0.697
SNP_A-8674898	1	204943515	rs11119342	MAPKAPK2	q32.1	0.232	0.546
SNP_A-8412643	1	204943960	rs12060808	MAPKAPK2	q32.1	0.405	0.158
SNP_A-8448630	1	204944397	rs6691678	MAPKAPK2	q32.1	0.233	0.573
SNP_A-8313470	1	204957058	rs6669284	MAPKAPK2	q32.1	0.325	0.293
SNP_A-8602038	1	204963373	rs4240848	MAPKAPK2	q32.1	0.212	0.053
SNP_A-8362304	1	204964104	rs4607880	MAPKAPK2	q32.1	0.212	0.049
SNP_A-2198036	1	204965675	rs11119385	MAPKAPK2	q32.1	0.324	0.266
SNP_A-8666515	1	207825250	rs17014830	CAMK1G	q32.2	0.188	0.168
SNP_A-8666517	1	207829498	rs11587591	CAMK1G	q32.2	0.312	0.199

SNP_A-2288939	1	207831499	rs7528476	CAMK1G	q32.2	0.323	0.407
SNP_A-2236830	1	207831616	rs7516885	CAMK1G	q32.2	0.189	0.200
SNP_A-8320366	1	207837970	rs9429821	CAMK1G	q32.2	0.378	0.371
SNP_A-8446064	1	207844298	rs17014866	CAMK1G	q32.2	0.146	0.373
SNP_A-8661823	1	207844716	rs2235452	CAMK1G	q32.2	0.152	0.827
SNP_A-8451997	1	207844906	rs2235453	CAMK1G	q32.2	0.150	0.726
SNP_A-8306040	1	207845978	rs12402938	CAMK1G	q32.2	0.150	0.993
SNP_A-8351700	1	207846011	rs2076224	CAMK1G	q32.2	0.263	0.368
SNP_A-2238360	1	207847371	rs760832	CAMK1G	q32.2	0.325	0.678
SNP_A-8630951	1	207847748	rs760833	CAMK1G	q32.2	0.185	0.579
SNP_A-4265019	1	207848451	rs10489339	CAMK1G	q32.2	0.147	0.141
SNP_A-4293077	1	207848966	rs11119314	CAMK1G	q32.2	0.376	0.904
SNP_A-2218232	2	39333719	rs3770675	MAP4K3	p22.1	0.092	0.382
SNP_A-2281853	2	39340050	rs7608958	MAP4K3	p22.1	0.167	0.437
SNP_A-2289659	2	39342336	rs10865148	MAP4K3	p22.1	0.163	0.458
SNP_A-8329880	2	39342942	rs10172736	MAP4K3	p22.1	0.086	0.226
SNP_A-1859895	2	39346789	rs3770670	MAP4K3	p22.1	0.085	0.425
SNP_A-8464261	2	39346825	rs17505544	MAP4K3	p22.1	0.365	0.837
SNP_A-4294761	2	39347701	rs2302749	MAP4K3	p22.1	0.167	0.625
SNP_A-1816658	2	39347973	rs10865149	MAP4K3	p22.1	0.090	0.319
SNP_A-2254407	2	39357195	rs7600014	MAP4K3	p22.1	0.082	0.339
SNP_A-2231943	2	39366439	rs7601700	MAP4K3	p22.1	0.083	0.343
SNP_A-2292431	2	39383380	rs10865150	MAP4K3	p22.1	0.078	0.475
SNP_A-4285622	2	39383640	rs3770664	MAP4K3	p22.1	0.180	0.543
SNP_A-1903005	2	39385585	rs7595469	MAP4K3	p22.1	0.167	0.286
SNP_A-2238618	2	39394518	rs11688352	MAP4K3	p22.1	0.450	0.738
SNP_A-8399053	2	39407880	rs2024514	MAP4K3	p22.1	0.155	0.522
SNP_A-8385013	2	39409448	rs9309036	MAP4K3	p22.1	0.170	0.532
SNP_A-2076719	2	39419076	rs4630750	MAP4K3	p22.1	0.114	0.711
SNP_A-1882720	2	39419339	rs1211996	MAP4K3	p22.1	0.106	0.476
SNP_A-4296109	2	39433881	rs2058863	MAP4K3	p22.1	0.141	0.934
SNP_A-1833820	2	39436950	rs7422651	MAP4K3	p22.1	0.108	0.440
SNP_A-4288549	2	39439768	rs2005892	MAP4K3	p22.1	0.091	0.347
SNP_A-8335477	2	39454226	rs6544221	MAP4K3	p22.1	0.137	0.894
SNP_A-1893857	2	39455393	rs17508058	MAP4K3	p22.1	0.105	0.724
SNP_A-8572875	2	39456220	rs10490305	MAP4K3	p22.1	0.053	0.166
SNP_A-8493114	2	39456454	rs11898704	MAP4K3	p22.1	0.060	0.113
SNP_A-4208015	2	39459421	rs2373530	MAP4K3	p22.1	0.078	0.680
SNP_A-2078677	2	39472170	rs4670932	MAP4K3	p22.1	0.102	0.134
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SNP_A-2141736	2	45733626	rs650508	PRKCE	p21	0.277	0.098
SNP_A-8573026	2	45741435	rs666214	PRKCE	p21	0.139	0.454
SNP_A-1843743	2	45752034	rs17033965	PRKCE	p21	0.139	0.312
SNP_A-8488309	2	45755619	rs17033973	PRKCE	p21	0.134	0.763
SNP_A-1916651	2	45755958	rs556650	PRKCE	p21	0.204	0.737
SNP_A-4240771	2	45759450	rs2204204	PRKCE	p21	0.236	0.281
SNP_A-2153368	2	45760818	rs3795863	PRKCE	p21	0.242	0.201
SNP_A-8316145	2	45762141	rs12185636	PRKCE	p21	0.278	0.385
SNP_A-2044493	2	45764120	rs2285024	PRKCE	p21	0.297	0.407
SNP_A-1963021	2	45764396	rs505310	PRKCE	p21	0.399	0.080
SNP_A-8573027	2	45769512	rs547018	PRKCE	p21	0.289	0.371
SNP_A-1963022	2	45769556	rs10490342	PRKCE	p21	0.128	0.940
SNP_A-1963023	2	45777789	rs612717	PRKCE	p21	0.194	0.206
SNP_A-1963024	2	45777848	rs10490341	PRKCE	p21	0.129	0.904
SNP_A-1953213	2	45780894	rs656823	PRKCE	p21	0.196	0.178
SNP_A-2098969	2	45782134	rs563601	PRKCE	p21	0.322	0.995
SNP_A-2184209	2	45783623	rs609573	PRKCE	p21	0.300	0.329
SNP_A-4223110	2	45785550	rs637889	PRKCE	p21	0.328	0.667
SNP_A-8396642	2	45786353	rs642200	PRKCE	p21	0.284	0.521
SNP_A-8440446	2	45788855	rs11677079	PRKCE	p21	0.193	0.115
SNP_A-1841802	2	45797830	rs1522986	PRKCE	p21	0.125	0.557
SNP_A-2187669	2	45797898	rs1522987	PRKCE	p21	0.124	0.560
SNP_A-1907487	2	45799725	rs6724488	PRKCE	p21	0.191	0.154
SNP_A-2194892	2	45800304	rs6725257	PRKCE	p21	0.189	0.204
SNP_A-8349655	2	45800613	rs6728564	PRKCE	p21	0.315	0.523
SNP_A-1963026	2	45807414	rs1464572	PRKCE	p21	0.362	0.594
SNP_A-2028324	2	45811755	rs10201978	PRKCE	p21	0.166	0.297
SNP_A-2166911	2	45813464	rs6743119	PRKCE	p21	0.469	0.914
SNP_A-8424861	2	45816505	rs6740453	PRKCE	p21	0.057	0.991
SNP_A-8458937	2	45817404	rs938659	PRKCE	p21	0.478	0.878
SNP_A-8707406	2	45818458	rs17034088	PRKCE	p21	0.059	0.906
SNP_A-8464919	2	45821800	rs10170642	PRKCE	p21	0.059	0.119
SNP_A-8692923	2	45821961	rs10170750	PRKCE	p21	0.448	0.302
SNP_A-8685544	2	45822684	rs7568380	PRKCE	p21	0.451	0.133

SNP_A-8314466	2	45827640	rs6716268	PRKCE	p21	0.305	0.608
SNP_A-8539881	2	45828359	rs6760916	PRKCE	p21	0.333	0.658
SNP_A-8625740	2	45829924	rs11125030	PRKCE	p21	0.335	0.764
SNP_A-8625225	2	45830086	rs11890554	PRKCE	p21	0.382	0.951
SNP_A-8399918	2	45830257	rs4953245	PRKCE	p21	0.496	0.600
SNP_A-8463542	2	45830976	rs6757543	PRKCE	p21	0.129	0.333
SNP_A-2270737	2	45835424	rs938661	PRKCE	p21	0.438	0.916
SNP_A-8643876	2	45835534	rs867286	PRKCE	p21	0.311	0.569
SNP_A-2249205	2	45836149	rs884400	PRKCE	p21	0.438	0.916
SNP_A-8699515	2	45837022	rs1468042	PRKCE	p21	0.441	0.725
SNP_A-8311894	2	45838890	rs4953247	PRKCE	p21	0.439	0.932
SNP_A-8681838	2	45839363	rs11684301	PRKCE	p21	0.200	0.680
SNP_A-8504792	2	45840123	rs4952769	PRKCE	p21	0.431	0.641
SNP_A-2244510	2	45842527	rs7582320	PRKCE	p21	0.340	0.429
SNP_A-8408275	2	45848267	rs4413199	PRKCE	p21	0.080	0.982
SNP_A-8581574	2	45848685	rs3924521	PRKCE	p21	0.096	0.554
SNP_A-8482745	2	45850161	rs13401638	PRKCE	p21	0.218	0.125
SNP_A-8309551	2	45850713	rs13404751	PRKCE	p21	0.297	0.525
SNP_A-4277706	2	45850915	rs13404973	PRKCE	p21	0.221	0.168
SNP_A-8714505	2	45850930	rs4953252	PRKCE	p21	0.315	0.770
SNP_A-2219885	2	45851023	rs13405086	PRKCE	p21	0.219	0.136
SNP_A-8301976	2	45852579	rs4953253	PRKCE	p21	0.235	0.386
SNP_A-1875937	2	45852620	rs4952771	PRKCE	p21	0.300	0.764
SNP_A-2108482	2	45853323	rs7577273	PRKCE	p21	0.366	0.271
SNP_A-8479487	2	45853990	rs6759058	PRKCE	p21	0.348	0.195
SNP_A-8582710	2	45854287	rs13002562	PRKCE	p21	0.350	0.143
SNP_A-8641157	2	45854929	rs6734661	PRKCE	p21	0.072	0.468
SNP_A-8312164	2	45855664	rs6753292	PRKCE	p21	0.263	0.052
SNP_A-1794832	2	45857497	rs4953254	PRKCE	p21	0.178	0.202
SNP_A-8573028	2	45869139	rs4074080	PRKCE	p21	0.338	0.326
SNP_A-1781277	2	45869355	rs7558342	PRKCE	p21	0.482	0.215
SNP_A-8520228	2	45871106	rs10170073	PRKCE	p21	0.424	0.381
SNP_A-8594886	2	45871727	rs11898074	PRKCE	p21	0.429	0.335
SNP_A-8674210	2	45880405	rs6743144	PRKCE	p21	0.484	0.341
SNP_A-8542134	2	45880921	rs12617104	PRKCE	p21	0.299	0.554
SNP_A-8483671	2	45881611	rs10164633	PRKCE	p21	0.216	0.637
SNP_A-8585356	2	45883745	rs3923011	PRKCE	p21	0.214	0.502
SNP_A-4252437	2	45887102	rs7591885	PRKCE	p21	0.476	0.325
SNP_A-8538858	2	45888916	rs11125033	PRKCE	p21	0.309	0.855
SNP_A-8703923	2	45892305	rs4296473	PRKCE	p21	0.113	0.219
SNP_A-4300528	2	45892651	rs7593800	PRKCE	p21	0.194	0.462
SNP_A-2267629	2	45894297	rs4953262	PRKCE	p21	0.464	0.229
SNP_A-1963027	2	45895982	rs3886870	PRKCE	p21	0.273	0.402
SNP_A-2023222	2	45899463	rs935672	PRKCE	p21	0.414	0.604
SNP_A-8449097	2	45902949	rs11125034	PRKCE	p21	0.116	0.603
SNP_A-8446713	2	45903353	rs7559151	PRKCE	p21	0.095	0.804
SNP_A-1869964	2	45904125	rs10179954	PRKCE	p21	0.375	0.719
SNP_A-8573029	2	45908642	rs2345182	PRKCE	p21	0.468	0.921
SNP_A-8573031	2	45908861	rs935661	PRKCE	p21	0.463	0.703
SNP_A-8377223	2	45909158	rs935658	PRKCE	p21	0.467	0.991
SNP_A-2077622	2	45910006	rs10865208	PRKCE	p21	0.461	0.786
SNP_A-8379997	2	45916054	rs6738409	PRKCE	p21	0.499	0.687
SNP_A-8497909	2	45917834	rs2345624	PRKCE	p21	0.483	0.581
SNP_A-1926317	2	45918361	rs935656	PRKCE	p21	0.159	0.267
SNP_A-8704542	2	45918460	rs2005270	PRKCE	p21	0.401	0.451
SNP_A-4253571	2	45918603	rs2005271	PRKCE	p21	0.441	0.794
SNP_A-4293707	2	45918963	rs2345625	PRKCE	p21	0.424	0.441
SNP_A-4205971	2	45919740	rs6732900	PRKCE	p21	0.425	0.934
SNP_A-2153034	2	45926828	rs4953269	PRKCE	p21	0.111	0.805
SNP_A-8385114	2	45926900	rs6761356	PRKCE	p21	0.285	0.553
SNP_A-8499302	2	45927156	rs4953270	PRKCE	p21	0.432	0.790
SNP_A-2057618	2	45927221	rs6719779	PRKCE	p21	0.316	0.125
SNP_A-4292842	2	45927600	rs4952782	PRKCE	p21	0.257	0.880
SNP_A-2098853	2	45928191	rs7593255	PRKCE	p21	0.246	0.041
SNP_A-2055057	2	45930542	rs10166692	PRKCE	p21	0.258	0.690
SNP_A-8688859	2	45931007	rs6756452	PRKCE	p21	0.111	0.872
SNP_A-2092484	2	45931967	rs6760363	PRKCE	p21	0.399	0.957
SNP_A-8571210	2	45933732	rs11890282	PRKCE	p21	0.277	0.481
SNP_A-2297143	2	45936374	rs4953273	PRKCE	p21	0.131	0.887
SNP_A-8548632	2	45936556	rs4953275	PRKCE	p21	0.218	0.190
SNP_A-8456389	2	45941377	rs1992932	PRKCE	p21	0.313	0.156
SNP_A-8327248	2	45941409	rs12465045	PRKCE	p21	0.137	0.855
SNP_A-2087913	2	45941456	rs1992933	PRKCE	p21	0.084	0.917
SNP_A-8548738	2	45941939	rs935652	PRKCE	p21	0.066	0.853

SNP_A-8692595	2	45944783	rs10181963	PRKCE	p21	0.214	0.068
SNP_A-4303647	2	45944962	rs4953279	PRKCE	p21	0.422	0.801
SNP_A-2218802	2	45947264	rs10189339	PRKCE	p21	0.326	0.148
SNP_A-8705554	2	45947928	rs4952786	PRKCE	p21	0.151	0.783
SNP_A-2154461	2	45947977	rs4952787	PRKCE	p21	0.152	0.832
SNP_A-8379918	2	45948309	rs11125037	PRKCE	p21	0.293	0.771
SNP_A-2100671	2	45949960	rs11125038	PRKCE	p21	0.327	0.363
SNP_A-8351373	2	45950307	rs12473396	PRKCE	p21	0.157	0.147
SNP_A-2058970	2	45951401	rs1966813	PRKCE	p21	0.454	0.165
SNP_A-8452206	2	45955645	rs12467641	PRKCE	p21	0.233	0.463
SNP_A-1923801	2	45955890	rs2881068	PRKCE	p21	0.366	0.475
SNP_A-1839631	2	45955956	rs2345178	PRKCE	p21	0.372	0.684
SNP_A-8365718	2	45960875	rs4953283	PRKCE	p21	0.359	0.444
SNP_A-2193058	2	45962015	rs13424270	PRKCE	p21	0.345	0.340
SNP_A-1947707	2	45962449	rs11125041	PRKCE	p21	0.231	0.361
SNP_A-8702919	2	45963339	rs935670	PRKCE	p21	0.418	0.747
SNP_A-8679037	2	45963929	rs735112	PRKCE	p21	0.343	0.368
SNP_A-8565862	2	45966520	rs2345179	PRKCE	p21	0.402	0.990
SNP_A-2292520	2	45971418	rs1982366	PRKCE	p21	0.348	0.378
SNP_A-8624077	2	45973894	rs4953286	PRKCE	p21	0.347	0.119
SNP_A-8498808	2	45974590	rs13400838	PRKCE	p21	0.066	0.642
SNP_A-8330297	2	45975668	rs10185201	PRKCE	p21	0.231	0.348
SNP_A-2236378	2	45979475	rs4953288	PRKCE	p21	0.369	0.590
SNP_A-8653561	2	45979919	rs4952792	PRKCE	p21	0.373	0.574
SNP_A-8707217	2	45980822	rs1463163	PRKCE	p21	0.328	0.614
SNP_A-8362548	2	45986364	rs13015067	PRKCE	p21	0.305	0.491
SNP_A-8506174	2	45986679	rs1868388	PRKCE	p21	0.434	0.740
SNP_A-4284222	2	45987295	rs878812	PRKCE	p21	0.300	0.458
SNP_A-8455113	2	45988269	rs935650	PRKCE	p21	0.296	0.262
SNP_A-8547560	2	45994308	rs13010241	PRKCE	p21	0.303	0.434
SNP_A-8412007	2	46006618	rs12986554	PRKCE	p21	0.482	0.264
SNP_A-8360270	2	46009575	rs6712478	PRKCE	p21	0.239	0.209
SNP_A-8604444	2	46012027	rs6720958	PRKCE	p21	0.097	0.404
SNP_A-1919468	2	46012194	rs13036100	PRKCE	p21	0.317	0.585
SNP_A-8594195	2	46016704	rs6544863	PRKCE	p21	0.390	0.586
SNP_A-8311718	2	46020799	rs2711300	PRKCE	p21	0.121	0.431
SNP_A-2285219	2	46022083	rs4953290	PRKCE	p21	0.208	0.754
SNP_A-1794308	2	46022433	rs2711292	PRKCE	p21	0.209	0.771
SNP_A-2121197	2	46023866	rs2029087	PRKCE	p21	0.121	0.997
SNP_A-8408299	2	46025740	rs2711297	PRKCE	p21	0.094	0.497
SNP_A-1864406	2	46026400	rs2711295	PRKCE	p21	0.089	0.657
SNP_A-8471870	2	46028240	rs13023787	PRKCE	p21	0.487	0.822
SNP_A-4257172	2	46029907	rs6750700	PRKCE	p21	0.307	0.581
SNP_A-1910466	2	46030466	rs6751349	PRKCE	p21	0.145	0.536
SNP_A-8654128	2	46033166	rs12471357	PRKCE	p21	0.431	0.312
SNP_A-4292746	2	46034497	rs2711293	PRKCE	p21	0.275	0.504
SNP_A-8600405	2	46036928	rs2711305	PRKCE	p21	0.498	0.276
SNP_A-1856634	2	46045228	rs2595201	PRKCE	p21	0.261	0.421
SNP_A-8549378	2	46045487	rs4953292	PRKCE	p21	0.480	0.809
SNP_A-8499092	2	46045521	rs2595202	PRKCE	p21	0.186	0.664
SNP_A-8472081	2	46045582	rs6759301	PRKCE	p21	0.057	0.461
SNP_A-8701655	2	46046851	rs6706140	PRKCE	p21	0.460	0.182
SNP_A-1897346	2	46054668	rs1868390	PRKCE	p21	0.243	0.514
SNP_A-1808507	2	46054841	rs1868392	PRKCE	p21	0.253	0.101
SNP_A-4284638	2	46055842	rs753572	PRKCE	p21	0.315	0.770
SNP_A-1886373	2	46058824	rs12464563	PRKCE	p21	0.423	0.499
SNP_A-4273239	2	46061122	rs7557421	PRKCE	p21	0.078	0.683
SNP_A-2113465	2	46061470	rs6705717	PRKCE	p21	0.451	0.935
SNP_A-2179029	2	46063632	rs2711286	PRKCE	p21	0.244	0.364
SNP_A-2152332	2	46065439	rs2595213	PRKCE	p21	0.235	0.289
SNP_A-8621963	2	46071174	rs2595214	PRKCE	p21	0.194	0.865
SNP_A-8308128	2	46074392	rs2711302	PRKCE	p21	0.163	0.901
SNP_A-8352791	2	46075259	rs12622193	PRKCE	p21	0.277	0.891
SNP_A-8611551	2	46081804	rs4952796	PRKCE	p21	0.304	0.726
SNP_A-1782219	2	46085546	rs2255094	PRKCE	p21	0.364	0.905
SNP_A-4292771	2	46085647	rs2255091	PRKCE	p21	0.157	0.912
SNP_A-2251120	2	46085876	rs2595222	PRKCE	p21	0.434	0.757
SNP_A-1844125	2	46086885	rs13016869	PRKCE	p21	0.174	0.814
SNP_A-2268227	2	46087174	rs11691705	PRKCE	p21	0.177	0.532
SNP_A-8329816	2	46087304	rs13423410	PRKCE	p21	0.056	0.955
SNP_A-4298954	2	46087623	rs10211547	PRKCE	p21	0.176	0.741
SNP_A-4242082	2	46088072	rs10188306	PRKCE	p21	0.178	0.679
SNP_A-2182022	2	46088863	rs7602129	PRKCE	p21	0.193	0.806
SNP_A-2063585	2	46090545	rs12465869	PRKCE	p21	0.265	0.219

SNP_A-8435640	2	46090713	rs4953299	PRKCE	p21	0.267	0.442
SNP_A-8690263	2	46098684	rs7593128	PRKCE	p21	0.399	0.426
SNP_A-2146316	2	46108254	rs13003856	PRKCE	p21	0.452	0.560
SNP_A-4287456	2	46109903	rs10167883	PRKCE	p21	0.170	0.286
SNP_A-1843184	2	46112445	rs11903923	PRKCE	p21	0.139	0.499
SNP_A-2257131	2	46113359	rs7573407	PRKCE	p21	0.404	0.314
SNP_A-8353442	2	46114320	rs6544869	PRKCE	p21	0.439	0.891
SNP_A-4246084	2	46127972	rs7563379	PRKCE	p21	0.408	0.405
SNP_A-8383980	2	46128167	rs6712036	PRKCE	p21	0.416	0.397
SNP_A-2006347	2	46130026	rs6748375	PRKCE	p21	0.443	0.465
SNP_A-2311276	2	46131427	rs12712960	PRKCE	p21	0.207	0.125
SNP_A-8564674	2	46138804	rs13001074	PRKCE	p21	0.245	0.503
SNP_A-8644491	2	46141058	rs12989656	PRKCE	p21	0.260	0.327
SNP_A-8701552	2	46141247	rs6751805	PRKCE	p21	0.207	0.274
SNP_A-8383761	2	46141357	rs6723478	PRKCE	p21	0.058	0.945
SNP_A-8709799	2	46143920	rs921183	PRKCE	p21	0.155	0.210
SNP_A-8541938	2	46146949	rs13405039	PRKCE	p21	0.112	0.941
SNP_A-8484624	2	46148315	rs12712962	PRKCE	p21	0.469	0.707
SNP_A-1833415	2	46148485	rs12712963	PRKCE	p21	0.384	0.670
SNP_A-8605587	2	46151346	rs6742625	PRKCE	p21	0.376	0.960
SNP_A-1813901	2	46152617	rs7598174	PRKCE	p21	0.209	0.213
SNP_A-8406687	2	46159906	rs2084428	PRKCE	p21	0.283	0.756
SNP_A-2159638	2	46164805	rs11125048	PRKCE	p21	0.355	0.406
SNP_A-4289329	2	46170608	rs1868273	PRKCE	p21	0.260	0.064
SNP_A-1850422	2	46170799	rs1868272	PRKCE	p21	0.261	0.201
SNP_A-2231388	2	46170852	rs1868271	PRKCE	p21	0.289	0.186
SNP_A-8509283	2	46173184	rs3768759	PRKCE	p21	0.156	0.214
SNP_A-8640495	2	46173506	rs3768758	PRKCE	p21	0.125	0.872
SNP_A-8573032	2	46174235	rs2345953	PRKCE	p21	0.351	0.847
SNP_A-1963028	2	46174384	rs2345955	PRKCE	p21	0.178	0.211
SNP_A-2305505	2	46174837	rs10202504	PRKCE	p21	0.177	0.138
SNP_A-8316189	2	46175944	rs4953307	PRKCE	p21	0.288	0.205
SNP_A-8567919	2	46176455	rs13024886	PRKCE	p21	0.391	0.872
SNP_A-8365676	2	46180173	rs3754574	PRKCE	p21	0.285	0.166
SNP_A-8331681	2	46180247	rs3754573	PRKCE	p21	0.288	0.145
SNP_A-8416000	2	46181682	rs4953313	PRKCE	p21	0.284	0.126
SNP_A-2221572	2	46198849	rs12616328	PRKCE	p21	0.193	0.428
SNP_A-2164393	2	46200220	rs3768751	PRKCE	p21	0.267	0.151
SNP_A-8414110	2	46200318	rs6719520	PRKCE	p21	0.102	0.137
SNP_A-8461212	2	46200527	rs3768750	PRKCE	p21	0.264	0.144
SNP_A-8608564	2	46201110	rs4952800	PRKCE	p21	0.259	0.186
SNP_A-1848141	2	46201296	rs2218660	PRKCE	p21	0.267	0.091
SNP_A-1963031	2	46205562	rs3768747	PRKCE	p21	0.317	0.375
SNP_A-1963032	2	46205830	rs17799476	PRKCE	p21	0.173	0.483
SNP_A-8573033	2	46205957	rs3754569	PRKCE	p21	0.436	0.363
SNP_A-8573034	2	46206003	rs10495927	PRKCE	p21	0.303	0.911
SNP_A-8692703	2	46210637	rs17737768	PRKCE	p21	0.110	0.828
SNP_A-8550770	2	46216181	rs10198247	PRKCE	p21	0.263	0.728
SNP_A-8471311	2	46219424	rs12992366	PRKCE	p21	0.082	0.544
SNP_A-1959365	2	46221800	rs4952803	PRKCE	p21	0.076	0.769
SNP_A-8643703	2	46223000	rs7563086	PRKCE	p21	0.073	0.304
SNP_A-2040701	2	46224718	rs3754568	PRKCE	p21	0.471	0.597
SNP_A-8292568	2	46225227	rs11690238	PRKCE	p21	0.171	0.744
SNP_A-1906052	2	46225258	rs6544873	PRKCE	p21	0.074	0.807
SNP_A-4261902	2	46225678	rs10495929	PRKCE	p21	0.140	0.093
SNP_A-1963035	2	46226779	rs1020445	PRKCE	p21	0.320	0.022
SNP_A-4261903	2	46227033	rs7604415	PRKCE	p21	0.083	0.709
SNP_A-2279112	2	46236903	rs4953321	PRKCE	p21	0.352	0.785
SNP_A-1909192	2	46237684	rs3754566	PRKCE	p21	0.137	0.387
SNP_A-1920555	2	46239475	rs6742742	PRKCE	p21	0.061	0.368
SNP_A-2075653	2	46239802	rs2034360	PRKCE	p21	0.153	0.447
SNP_A-1952633	2	46250099	rs11690929	PRKCE	p21	0.133	0.725
SNP_A-8573035	2	46251135	rs951012	PRKCE	p21	0.284	0.993
SNP_A-8628854	2	46252070	rs281479	PRKCE	p21	0.071	0.195
SNP_A-1786227	2	46257341	rs281472	PRKCE	p21	0.075	0.149
SNP_A-2027087	2	46257393	rs281471	PRKCE	p21	0.061	0.369
SNP_A-4198300	2	46258349	rs10210199	PRKCE	p21	0.182	0.881
SNP_A-2024817	2	46259338	rs281469	PRKCE	p21	0.183	0.479
SNP_A-8487754	2	46261198	rs281467	PRKCE	p21	0.186	0.866
SNP_A-2210573	2	46261432	rs1448219	PRKCE	p21	0.064	0.306
SNP_A-8435627	2	46261575	rs2594489	PRKCE	p21	0.364	0.767
SNP_A-1936910	2	46261844	rs2594491	PRKCE	p21	0.490	0.439
SNP_A-8418906	2	46261925	rs2594492	PRKCE	p21	0.489	0.272
SNP_A-1963036	2	46264711	rs281508	PRKCE	p21	0.284	0.826

SNP_A-2263538	2	101687072	rs17809691	MAP4K4	q11.2	0.309	0.576
SNP_A-8470241	2	101689196	rs6734799	MAP4K4	q11.2	0.281	0.856
SNP_A-2224053	2	101717462	rs7597661	MAP4K4	q11.2	0.063	0.752
SNP_A-2069713	2	101726355	rs4384813	MAP4K4	q11.2	0.078	0.876
SNP_A-8400129	2	101733994	rs17810475	MAP4K4	q11.2	0.311	0.659
SNP_A-8517670	2	101741391	rs11123901	MAP4K4	q11.2	0.333	0.763
SNP_A-1828557	2	101763395	rs11683001	MAP4K4	q11.2	0.292	0.429
SNP_A-8648410	2	101779018	rs6543095	MAP4K4	q11.2	0.076	0.742
SNP_A-8661331	2	101781569	rs11887131	MAP4K4	q11.2	0.064	0.739
SNP_A-2155959	2	101788410	rs6732726	MAP4K4	q11.2	0.294	0.363
SNP_A-4196055	2	101796069	rs17026143	MAP4K4	q11.2	0.060	0.395
SNP_A-8454396	2	101805268	rs875565	MAP4K4	q11.2	0.309	0.576
SNP_A-8575777	2	101810253	rs2236936	MAP4K4	q11.2	0.324	0.646
SNP_A-8575778	2	101810474	rs2236935	MAP4K4	q11.2	0.243	0.758
SNP_A-2274480	2	101829006	rs17802002	MAP4K4	q11.2	0.146	0.063
SNP_A-4208258	2	101832572	rs10489973	MAP4K4	q11.2	0.144	0.043
SNP_A-1918300	2	101834055	rs2158816	MAP4K4	q11.2	0.462	0.559
SNP_A-8306451	2	101844784	rs13425874	MAP4K4	q11.2	0.064	0.726
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SNP_A-2236284	2	101862349	rs4851507	MAP4K4	q11.2	0.471	0.569
SNP_A-4208259	2	101870995	rs11895969	MAP4K4	q11.2	0.062	0.786
SNP_A-4279539	2	101872136	rs7574674	MAP4K4	q11.2	0.076	0.805
SNP_A-4235988	2	127787473	rs6731176	MAP3K2	q14.3	0.438	0.552
SNP_A-1811257	3	48762223	rs6791542	PRKAR2A	p21.31	0.359	0.444
SNP_A-1894572	3	48812186	rs9859473	PRKAR2A	p21.31	0.246	0.375
SNP_A-8716957	3	49877164	rs2883059	CAMKV	p21.31	0.380	0.583
SNP_A-4281355	3	50626755	rs873985	MAPKAPK3	p21.31	0.136	0.619
SNP_A-2237373	3	50645082	rs2040397	MAPKAPK3	p21.31	0.283	0.187
SNP_A-8700373	3	50659815	rs11711534	MAPKAPK3	p21.31	0.066	0.279
SNP_A-2272004	3	53174054	rs1483185	PRKCD	p21.1	0.145	0.985
SNP_A-1888152	3	53174120	rs1483186	PRKCD	p21.1	0.114	0.672
SNP_A-8319598	3	53176938	rs750170	PRKCD	p21.1	0.150	0.344
SNP_A-8402522	3	53183957	rs3821689	PRKCD	p21.1	0.352	0.296
SNP_A-1954339	3	53187756	rs17052826	PRKCD	p21.1	0.157	0.589
SNP_A-8295445	3	53188697	rs2230493	PRKCD	p21.1	0.160	0.708
SNP_A-2097191	3	53191732	rs13084863	PRKCD	p21.1	0.484	0.483
SNP_A-8519453	3	171430600	rs1082969	PRKCI	q26.2	0.177	0.352
SNP_A-2039928	3	171441246	rs1684885	PRKCI	q26.2	0.184	0.194
SNP_A-8421754	3	171454775	rs2650229	PRKCI	q26.2	0.197	0.206
SNP_A-4199928	3	171473104	rs2140825	PRKCI	q26.2	0.374	0.229
SNP_A-8516417	3	171505189	rs2650220	PRKCI	q26.2	0.179	0.117
SNP_A-2031710	3	186505879	rs9875687	MAP3K13	q27.2	0.162	0.577
SNP_A-4261414	3	186508583	rs6779106	MAP3K13	q27.2	0.214	0.826
SNP_A-2042951	3	186509681	rs9830680	MAP3K13	q27.2	0.164	0.891
SNP_A-2026229	3	186512797	rs7631503	MAP3K13	q27.2	0.164	0.917
SNP_A-4279123	3	186514488	rs7431357	MAP3K13	q27.2	0.163	0.845
SNP_A-8306082	3	186525017	rs12639437	MAP3K13	q27.2	0.096	0.048
SNP_A-8549560	3	186531008	rs7432658	MAP3K13	q27.2	0.214	0.362
SNP_A-8443302	3	186535467	rs9871486	MAP3K13	q27.2	0.169	0.613
SNP_A-2298462	3	186545134	rs6444052	MAP3K13	q27.2	0.405	0.269
SNP_A-8391906	3	186560578	rs12492085	MAP3K13	q27.2	0.189	0.293
SNP_A-4275982	3	186573513	rs9847739	MAP3K13	q27.2	0.383	0.371
SNP_A-8352138	3	186581213	rs13076191	MAP3K13	q27.2	0.293	0.861
SNP_A-2208974	3	186584193	rs12163582	MAP3K13	q27.2	0.257	0.836
SNP_A-2093375	3	186587758	rs6444062	MAP3K13	q27.2	0.071	0.491
SNP_A-1845462	3	186594994	rs4687296	MAP3K13	q27.2	0.224	0.841
SNP_A-1858626	3	186606110	rs6803944	MAP3K13	q27.2	0.155	0.973
SNP_A-1842085	3	186607301	rs9842230	MAP3K13	q27.2	0.162	0.399
SNP_A-8560253	3	186617799	rs7646178	MAP3K13	q27.2	0.153	0.897
SNP_A-8357664	3	186623829	rs12490248	MAP3K13	q27.2	0.069	0.228
SNP_A-8364346	3	186634807	rs1017501	MAP3K13	q27.2	0.286	0.397
SNP_A-2208154	3	186638176	rs2304815	MAP3K13	q27.2	0.162	0.158
SNP_A-4289058	3	186645679	rs12053946	MAP3K13	q27.2	0.104	0.468
SNP_A-8447463	3	186663506	rs9878704	MAP3K13	q27.2	0.130	0.397
SNP_A-8566075	3	186666776	rs13095772	MAP3K13	q27.2	0.095	0.116
SNP_A-4210268	4	71147663	rs3775745	CSN3	q13.3	0.400	0.244
SNP_A-1977526	4	71148222	rs10518071	CSN3	q13.3	0.159	0.418
SNP_A-8531795	4	71149545	rs1048152	CSN3	q13.3	0.080	0.557
SNP_A-8332095	4	71149832	rs3775737	CSN3	q13.3	0.106	0.425
SNP_A-8461131	4	71149921	rs3822164	CSN3	q13.3	0.161	0.397
SNP_A-1877976	4	71150849	rs41508150	CSN3	q13.3	0.158	0.299
SNP_A-1931763	4	71151123	rs13141970	CSN3	q13.3	0.238	0.799
SNP_A-1818187	4	71151212	rs41523244	CSN3	q13.3	0.158	0.289
SNP_A-8463788	4	87156898	rs958	MAPK10	q21.3	0.197	0.039

SNP_A-2244414	4	87165708	rs3775168	MAPK10	q21.3	0.183	0.523
SNP_A-2105720	4	87172931	rs6848433	MAPK10	q21.3	0.117	0.587
SNP_A-8569188	4	87173891	rs3775173	MAPK10	q21.3	0.141	0.834
SNP_A-4297480	4	87182808	rs4351013	MAPK10	q21.3	0.177	0.448
SNP_A-2129317	4	87184667	rs10033283	MAPK10	q21.3	0.113	0.714
SNP_A-1977930	4	87185127	rs6810413	MAPK10	q21.3	0.418	0.504
SNP_A-8363883	4	87189425	rs17008675	MAPK10	q21.3	0.172	0.619
SNP_A-2248883	4	87194086	rs17011341	MAPK10	q21.3	0.113	0.714
SNP_A-8316838	4	87202256	rs3775187	MAPK10	q21.3	0.419	0.437
SNP_A-2262246	4	87230328	rs4482754	MAPK10	q21.3	0.416	0.461
SNP_A-1840361	4	87233830	rs12502934	MAPK10	q21.3	0.418	0.414
SNP_A-8409777	4	87238262	rs9884770	MAPK10	q21.3	0.416	0.352
SNP_A-8323126	4	87240962	rs12644947	MAPK10	q21.3	0.365	0.887
SNP_A-8641574	4	87248708	rs12647176	MAPK10	q21.3	0.161	0.585
SNP_A-8466205	4	87256403	rs5006575	MAPK10	q21.3	0.142	0.426
SNP_A-4260434	4	87268401	rs4546235	MAPK10	q21.3	0.317	0.142
SNP_A-1799957	4	87283699	rs4693757	MAPK10	q21.3	0.143	0.825
SNP_A-8430016	4	87291488	rs4334746	MAPK10	q21.3	0.319	0.883
SNP_A-1787687	4	87293056	rs10001480	MAPK10	q21.3	0.164	0.499
SNP_A-1853382	4	87293272	rs10024003	MAPK10	q21.3	0.155	0.785
SNP_A-8662194	4	87318361	rs2199308	MAPK10	q21.3	0.194	0.745
SNP_A-1977931	4	87323194	rs10516769	MAPK10	q21.3	0.124	0.884
SNP_A-1977932	4	87326932	rs1460767	MAPK10	q21.3	0.292	0.645
SNP_A-2071922	4	87327534	rs7668374	MAPK10	q21.3	0.211	0.893
SNP_A-2044365	4	87356659	rs10026060	MAPK10	q21.3	0.153	0.454
SNP_A-8590056	4	87357762	rs12650052	MAPK10	q21.3	0.135	0.928
SNP_A-1812112	4	87357789	rs10029339	MAPK10	q21.3	0.219	0.696
SNP_A-2009966	4	87366528	rs6827698	MAPK10	q21.3	0.218	0.786
SNP_A-2135450	4	87385929	rs17011584	MAPK10	q21.3	0.136	0.842
SNP_A-8662195	4	87391122	rs10516770	MAPK10	q21.3	0.065	0.337
SNP_A-8662196	4	87401460	rs9307016	MAPK10	q21.3	0.153	0.660
SNP_A-8463636	4	87403238	rs6531914	MAPK10	q21.3	0.277	0.459
SNP_A-8330548	4	87427125	rs17011659	MAPK10	q21.3	0.114	0.413
SNP_A-8323506	4	87440504	rs6827098	MAPK10	q21.3	0.370	0.412
SNP_A-8518424	4	87440851	rs17449015	MAPK10	q21.3	0.090	0.977
SNP_A-8472385	4	87442492	rs1460753	MAPK10	q21.3	0.369	0.329
SNP_A-2265728	4	87462364	rs6856688	MAPK10	q21.3	0.153	0.454
SNP_A-2244713	4	87466341	rs9994931	MAPK10	q21.3	0.239	0.902
SNP_A-2101945	4	87471283	rs4693142	MAPK10	q21.3	0.239	0.892
SNP_A-8687155	4	87471821	rs7677400	MAPK10	q21.3	0.122	0.721
SNP_A-8676896	4	87475230	rs17409904	MAPK10	q21.3	0.482	0.273
SNP_A-8440185	4	87475280	rs17409925	MAPK10	q21.3	0.270	0.110
SNP_A-4240279	4	87475647	rs6825707	MAPK10	q21.3	0.228	0.620
SNP_A-4224821	4	87478030	rs4611890	MAPK10	q21.3	0.490	0.231
SNP_A-8469663	4	87478062	rs2869431	MAPK10	q21.3	0.270	0.105
SNP_A-4279963	4	87481803	rs11097106	MAPK10	q21.3	0.231	0.802
SNP_A-8713050	4	87482275	rs17011756	MAPK10	q21.3	0.395	0.738
SNP_A-2261773	4	87485320	rs4693765	MAPK10	q21.3	0.240	0.934
SNP_A-1862859	4	87485480	rs4693766	MAPK10	q21.3	0.238	0.842
SNP_A-2101504	4	87488367	rs11097109	MAPK10	q21.3	0.237	0.940
SNP_A-2188621	4	87493198	rs17451111	MAPK10	q21.3	0.341	0.332
SNP_A-8662200	4	87509948	rs2869438	PTPN13	q21.3	0.242	0.718
SNP_A-8390131	4	87516818	rs17011843	PTPN13	q21.3	0.150	0.483
SNP_A-1977938	4	87522688	rs9307018	PTPN13	q21.3	0.394	0.635
SNP_A-2083303	4	87559754	rs11938088	PTPN13	q21.3	0.186	0.490
SNP_A-8700436	4	87581858	rs4488910	PTPN13	q21.3	0.140	0.330
SNP_A-8647612	4	87588087	rs12503051	PTPN13	q21.3	0.150	0.501
SNP_A-8366082	4	87597820	rs4693770	PTPN13	q21.3	0.113	0.753
SNP_A-8478575	4	87608141	rs7658485	PTPN13	q21.3	0.373	0.167
SNP_A-1843910	4	87632205	rs9683663	PTPN13	q21.3	0.272	0.561
SNP_A-2258439	4	87632448	rs2869441	PTPN13	q21.3	0.142	0.139
SNP_A-8622649	4	87633587	rs17418801	PTPN13	q21.3	0.273	0.683
SNP_A-1977939	4	87636315	rs6838659	PTPN13	q21.3	0.328	0.639
SNP_A-8646069	4	87643363	rs4640633	PTPN13	q21.3	0.332	0.824
SNP_A-8548526	4	87653746	rs4552430	PTPN13	q21.3	0.324	0.617
SNP_A-8663293	4	114603777	rs17620390	CAMK2D	q26	0.242	0.341
SNP_A-8663294	4	114610853	rs6835747	CAMK2D	q26	0.145	0.528
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SNP_A-1978573	4	114612078	rs6842886	CAMK2D	q26	0.174	0.634
SNP_A-2075048	4	114613293	rs17629820	CAMK2D	q26	0.063	0.778
SNP_A-1955210	4	114620118	rs4834340	CAMK2D	q26	0.381	0.736
SNP_A-8580743	4	114624559	rs11936225	CAMK2D	q26	0.142	0.619
SNP_A-8612434	4	114636045	rs2158196	CAMK2D	q26	0.493	0.227
SNP_A-2054194	4	114636070	rs2158197	CAMK2D	q26	0.466	0.521

SNP_A-8396214	4	114637591	rs757174	CAMK2D	q26	0.474	0.502
SNP_A-1919560	4	114641161	rs17446453	CAMK2D	q26	0.238	0.379
SNP_A-4210464	4	114645147	rs7684265	CAMK2D	q26	0.106	0.977
SNP_A-2069735	4	114645383	rs4834347	CAMK2D	q26	0.229	0.205
SNP_A-2030907	4	114648856	rs11098193	CAMK2D	q26	0.232	0.240
SNP_A-2033497	4	114651522	rs17046126	CAMK2D	q26	0.299	0.321
SNP_A-1959757	4	114651703	rs17630012	CAMK2D	q26	0.062	0.786
SNP_A-1825329	4	114655326	rs3815072	CAMK2D	q26	0.141	0.956
SNP_A-1954201	4	114656174	rs13146211	CAMK2D	q26	0.260	0.979
SNP_A-2290032	4	114672173	rs4240286	CAMK2D	q26	0.439	0.220
SNP_A-8405706	4	114697931	rs11724156	CAMK2D	q26	0.250	0.573
SNP_A-8309838	4	114698102	rs11728021	CAMK2D	q26	0.154	0.314
SNP_A-4224250	4	114700740	rs17630328	CAMK2D	q26	0.076	0.621
SNP_A-8701995	4	114706327	rs7673652	CAMK2D	q26	0.055	0.148
SNP_A-1914742	4	114715426	rs10009286	CAMK2D	q26	0.320	0.423
SNP_A-2183689	4	114715574	rs13144613	CAMK2D	q26	0.348	0.971
SNP_A-1978576	4	114718478	rs6533700	CAMK2D	q26	0.254	0.447
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SNP_A-8448606	4	114721072	rs13130904	CAMK2D	q26	0.093	0.522
SNP_A-8704161	4	114721621	rs7666890	CAMK2D	q26	0.279	0.639
SNP_A-1845850	4	114723041	rs11946664	CAMK2D	q26	0.301	0.127
SNP_A-1978579	4	114723610	rs17531554	CAMK2D	q26	0.142	0.139
SNP_A-1978580	4	114723767	rs10488894	CAMK2D	q26	0.298	0.140
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SNP_A-2039515	4	114727378	rs1859148	CAMK2D	q26	0.254	0.515
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SNP_A-2133337	4	114730973	rs1859150	CAMK2D	q26	0.306	0.079
SNP_A-2119867	4	114731586	rs17531701	CAMK2D	q26	0.109	0.081
SNP_A-2290555	4	114732225	rs6533701	CAMK2D	q26	0.301	0.182
SNP_A-2244351	4	114732247	rs6821520	CAMK2D	q26	0.087	0.064
SNP_A-8663298	4	114754172	rs10488958	CAMK2D	q26	0.249	0.476
SNP_A-4203624	4	114762663	rs6826859	CAMK2D	q26	0.147	0.169
SNP_A-2194314	4	114762869	rs1047187	CAMK2D	q26	0.222	0.410
SNP_A-8637708	4	114763632	rs7676656	CAMK2D	q26	0.496	0.137
SNP_A-1796746	4	114763744	rs7676842	CAMK2D	q26	0.367	0.842
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SNP_A-4221121	4	114766153	rs10023113	CAMK2D	q26	0.133	0.016
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SNP_A-8663303	4	114828167	rs2214457	CAMK2D	q26	0.058	0.448
SNP_A-8376876	4	114838051	rs987694	CAMK2D	q26	0.379	0.308
SNP_A-4218908	4	114838837	rs12508566	CAMK2D	q26	0.382	0.264
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SNP_A-1908116	4	114853816	rs12644009	CAMK2D	q26	0.380	0.208
SNP_A-8552803	4	114881130	rs1859229	CAMK2D	q26	0.252	0.273
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SNP_A-8453521	5	40818671	rs3805494	PRKAA1	p13.1	0.259	0.772
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SNP_A-2148064	5	56149199	rs1423622	MAP3K1	q11.2	0.087	0.098
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SNP_A-1981663	5	56154632	rs252905	MAP3K1	q11.2	0.372	0.101
SNP_A-1981664	5	56154947	rs252906	MAP3K1	q11.2	0.375	0.171

SNP_A-1981665	5	56157511	rs252915	MAP3K1	q11.2	0.175	0.777
SNP_A-8525153	5	56158101	rs16886364	MAP3K1	q11.2	0.062	0.681
SNP_A-4225141	5	56164756	rs863840	MAP3K1	q11.2	0.182	0.700
SNP_A-1863183	5	56175003	rs16886403	MAP3K1	q11.2	0.129	0.193
SNP_A-1981667	5	56185186	rs860580	MAP3K1	q11.2	0.176	0.764
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SNP_A-1917357	5	56197544	rs832575	MAP3K1	q11.2	0.120	0.664
SNP_A-1981669	5	56206570	rs16886448	MAP3K1	q11.2	0.064	0.749
SNP_A-2266319	5	56214969	rs832584	MAP3K1	q11.2	0.177	0.728
SNP_A-8616379	5	56222832	rs860579	MAP3K1	q11.2	0.057	0.469
SNP_A-1880422	5	68691891	rs6450035	TAF9	q13.2	0.086	0.190
SNP_A-8584394	5	68692083	rs2010352	TAF9	q13.2	0.429	0.226
SNP_A-1982915	5	110590399	rs727922	CAMK4	q22.1	0.244	0.982
SNP_A-8478745	5	110591764	rs10077974	CAMK4	q22.1	0.074	0.839
SNP_A-8510417	5	110595497	rs1457115	CAMK4	q22.1	0.456	0.800
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SNP_A-4211168	5	110596399	rs9326832	CAMK4	q22.1	0.270	0.413
SNP_A-1813210	5	110598075	rs17461314	CAMK4	q22.1	0.271	0.947
SNP_A-8362268	5	110607340	rs2052859	CAMK4	q22.1	0.334	0.748
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SNP_A-8665944	5	110613526	rs712645	CAMK4	q22.1	0.453	0.360
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SNP_A-8328625	5	110619629	rs1650796	CAMK4	q22.1	0.271	0.378
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SNP_A-8509812	5	110629622	rs1644496	CAMK4	q22.1	0.468	0.762
SNP_A-2235314	5	110633954	rs1618689	CAMK4	q22.1	0.261	0.685
SNP_A-2251301	5	110634040	rs2288397	CAMK4	q22.1	0.194	0.107
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SNP_A-1900904	5	110694303	rs1644505	CAMK4	q22.1	0.464	0.660
SNP_A-2186047	5	110696315	rs2560495	CAMK4	q22.1	0.425	0.911
SNP_A-8652063	5	110696599	rs1650782	CAMK4	q22.1	0.464	0.579
SNP_A-1822244	5	110705949	rs375359	CAMK4	q22.1	0.379	0.467
SNP_A-2011137	5	110707556	rs446176	CAMK4	q22.1	0.120	0.764
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SNP_A-4211169	5	110714128	rs434256	CAMK4	q22.1	0.120	0.743
SNP_A-8621975	5	110716145	rs534608	CAMK4	q22.1	0.119	0.780
SNP_A-1841051	5	110717621	rs387551	CAMK4	q22.1	0.118	0.806
SNP_A-8712021	5	110718462	rs376880	CAMK4	q22.1	0.119	0.799
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SNP_A-2246001	5	110729426	rs450315	CAMK4	q22.1	0.117	0.562
SNP_A-2011138	5	110730506	rs388944	CAMK4	q22.1	0.112	0.492
SNP_A-8504443	5	110731528	rs1470168	CAMK4	q22.1	0.429	0.789
SNP_A-1931308	5	110731617	rs438178	CAMK4	q22.1	0.116	0.369
SNP_A-1852217	5	110751259	rs306109	CAMK4	q22.1	0.097	0.536
SNP_A-1940325	5	110751280	rs306108	CAMK4	q22.1	0.108	0.596
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SNP_A-2164855	5	110791508	rs4957949	CAMK4	q22.1	0.365	0.130
SNP_A-8451556	5	110791945	rs10045295	CAMK4	q22.1	0.375	0.086
SNP_A-8655553	5	110792151	rs10039731	CAMK4	q22.1	0.412	0.417
SNP_A-1982922	5	110798955	rs1820666	CAMK4	q22.1	0.295	0.654
SNP_A-4157790	5	110800303	rs10491334	CAMK4	q22.1	0.173	0.333
SNP_A-1982923	5	110800619	rs759950	CAMK4	q22.1	0.394	0.227
SNP_A-4211170	5	110800828	rs759949	CAMK4	q22.1	0.402	0.388
SNP_A-4211171	5	110800841	rs759948	CAMK4	q22.1	0.374	0.188
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SNP_A-1982924	5	110801072	rs7736139	CAMK4	q22.1	0.250	0.124
SNP_A-1945603	5	110801356	rs11241123	CAMK4	q22.1	0.401	0.498
SNP_A-1982925	5	110801595	rs4957951	CAMK4	q22.1	0.389	0.121
SNP_A-4211173	5	110802124	rs9326835	CAMK4	q22.1	0.292	0.169
SNP_A-8656721	5	110802842	rs10066487	CAMK4	q22.1	0.209	0.065
SNP_A-8637287	5	110805439	rs31328	CAMK4	q22.1	0.197	0.077

SNP_A-8697091	5	110808194	rs4957952	CAMK4	q22.1	0.473	0.785
SNP_A-2296065	5	110809436	rs17458552	CAMK4	q22.1	0.348	0.187
SNP_A-2154125	5	110814621	rs1897528	CAMK4	q22.1	0.427	0.616
SNP_A-8563300	5	110815528	rs971193	CAMK4	q22.1	0.427	0.801
SNP_A-4217621	5	110815887	rs31317	CAMK4	q22.1	0.097	0.563
SNP_A-2207027	5	110815911	rs17536705	CAMK4	q22.1	0.307	0.581
SNP_A-8351774	5	110822269	rs2268944	CAMK4	q22.1	0.424	0.481
SNP_A-1982926	5	110840940	rs31623	CAMK4	q22.1	0.125	0.913
SNP_A-8595498	5	110841556	rs10055516	CAMK4	q22.1	0.462	0.555
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SNP_A-4289261	5	149585404	rs4958468	CAMK2A	q33.1	0.063	0.318
SNP_A-2227932	5	149585481	rs4958467	CAMK2A	q33.1	0.267	0.104
SNP_A-8356150	5	149586941	rs10051644	CAMK2A	q33.1	0.285	0.824
SNP_A-8714035	5	149590165	rs1549913	CAMK2A	q33.1	0.413	0.929
SNP_A-2107044	5	149595874	rs10066581	CAMK2A	q33.1	0.125	0.185
SNP_A-4197534	5	149595967	rs17111079	CAMK2A	q33.1	0.099	0.689
SNP_A-8707384	5	149618553	rs4958445	CAMK2A	q33.1	0.271	0.802
SNP_A-8497551	5	149620473	rs882282	CAMK2A	q33.1	0.100	0.957
SNP_A-4265298	5	149621348	rs3822606	CAMK2A	q33.1	0.274	0.906
SNP_A-2250584	5	149637560	rs34087853	CAMK2A	q33.1	0.263	0.571
SNP_A-4242123	5	149640783	rs6881743	CAMK2A	q33.1	0.260	0.780
SNP_A-1899345	5	149641142	rs10050608	CAMK2A	q33.1	0.244	0.800
SNP_A-4300146	5	149641346	rs1432833	CAMK2A	q33.1	0.243	0.929
SNP_A-2236390	5	149647471	rs4958869	CAMK2A	q33.1	0.250	0.925
SNP_A-2011492	5	179596220	rs6601104	MAPK9	q35.3	0.424	0.365
SNP_A-1804851	5	179602877	rs4639174	MAPK9	q35.3	0.161	0.555
SNP_A-8511864	5	179603134	rs7445806	MAPK9	q35.3	0.426	0.122
SNP_A-2153896	5	179609267	rs11743623	MAPK9	q35.3	0.073	0.176
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SNP_A-8541998	5	179610123	rs4147385	MAPK9	q35.3	0.218	0.175
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SNP_A-8358377	5	179612839	rs11249687	MAPK9	q35.3	0.080	0.285
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SNP_A-2023565	5	179626784	rs17627880	MAPK9	q35.3	0.231	0.492
SNP_A-8681017	5	179630108	rs3095944	MAPK9	q35.3	0.322	0.570
SNP_A-8520884	5	179637509	rs730688	MAPK9	q35.3	0.259	0.182
SNP_A-8443507	5	179641502	rs3812066	MAPK9	q35.3	0.200	0.122
SNP_A-8584040	5	179644666	rs6867398	MAPK9	q35.3	0.266	0.283
SNP_A-2261079	6	36110440	rs16883860	MAPK14	p21.31	0.090	0.140
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SNP_A-8670790	6	36127205	rs664367	MAPK14	p21.31	0.476	0.985
SNP_A-1985684	6	36127314	rs17714205	MAPK14	p21.31	0.127	0.462
SNP_A-1985685	6	36143332	rs2237093	MAPK14	p21.31	0.101	0.407
SNP_A-2154502	6	36165946	rs16884628	MAPK14	p21.31	0.096	0.897
SNP_A-8536609	6	36170969	rs7771484	MAPK14	p21.31	0.091	0.325
SNP_A-2011706	6	36176281	rs7761118	MAPK14	p21.31	0.091	1.000
SNP_A-2046777	6	36179495	rs16884919	MAPK14	p21.31	0.096	0.897
SNP_A-8414404	6	36183888	rs12530381	MAPK14	p21.31	0.482	0.723
SNP_A-2108498	6	36184912	rs3804452	MAPK14	p21.31	0.129	0.557
SNP_A-4292466	6	36208710	rs2071864	MAPK13	p21.31	0.292	0.359
SNP_A-4255072	6	91288073	rs3799917	MAP3K7	q15	0.312	0.669
SNP_A-1838284	6	91288700	rs205339	MAP3K7	q15	0.258	0.817
SNP_A-1986819	6	91295724	rs150125	MAP3K7	q15	0.256	0.728
SNP_A-4290463	6	91304421	rs1144159	MAP3K7	q15	0.195	0.402
SNP_A-8527867	6	91305464	rs3799912	MAP3K7	q15	0.122	0.030
SNP_A-2101372	6	91305939	rs205352	MAP3K7	q15	0.261	0.423
SNP_A-8670822	6	91306072	rs205351	MAP3K7	q15	0.263	0.914
SNP_A-2022236	6	91310473	rs1145728	MAP3K7	q15	0.340	0.254
SNP_A-2260776	6	91313649	rs2273567	MAP3K7	q15	0.313	0.399
SNP_A-2116248	6	91336830	rs1143794	MAP3K7	q15	0.340	0.207
SNP_A-1936150	6	122839383	rs9388077	PKIB	q22.31	0.149	0.674
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SNP_A-8317720	6	122842681	rs544099	PKIB	q22.31	0.282	0.526
SNP_A-2178910	6	122845811	rs561470	PKIB	q22.31	0.434	0.218
SNP_A-8499664	6	122853798	rs9398675	PKIB	q22.31	0.078	0.685
SNP_A-1816529	6	122873901	rs9490464	PKIB	q22.31	0.150	0.726
SNP_A-2303880	6	122894532	rs9385257	PKIB	q22.31	0.148	0.638
SNP_A-1821815	6	122898087	rs9320876	PKIB	q22.31	0.149	0.610
SNP_A-4193548	6	122920535	rs197687	PKIB	q22.31	0.322	0.343
SNP_A-8669574	6	122929254	rs9375150	PKIB	q22.31	0.431	0.319
SNP_A-4250066	6	122938979	rs9398678	PKIB	q22.31	0.141	0.466
SNP_A-8538077	6	122963824	rs9385261	PKIB	q22.31	0.135	0.349
SNP_A-8513513	6	122968759	rs13191198	PKIB	q22.31	0.436	0.349
SNP_A-8331254	6	122976860	rs9388103	PKIB	q22.31	0.118	0.856

SNP_A-8414613	6	122979068	rs17675201	PKIB	q22.31	0.262	0.149
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SNP_A-8413789	6	122979311	rs9320884	PKIB	q22.31	0.307	0.816
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SNP_A-2153510	6	123001204	rs17084680	PKIB	q22.31	0.292	0.640
SNP_A-2269731	6	123008805	rs2566833	PKIB	q22.31	0.319	0.108
SNP_A-2240713	6	123009857	rs13215891	PKIB	q22.31	0.064	0.320
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SNP_A-8378945	6	123015131	rs13193040	PKIB	q22.31	0.330	0.614
SNP_A-8676901	6	123019230	rs9401564	PKIB	q22.31	0.113	0.753
SNP_A-2248031	6	123022210	rs7752438	PKIB	q22.31	0.330	0.658
SNP_A-8704114	6	123022258	rs17052989	PKIB	q22.31	0.093	0.432
SNP_A-2257821	6	123024190	rs11154103	PKIB	q22.31	0.292	0.645
SNP_A-8669575	6	123040291	rs7769704	PKIB	q22.31	0.336	0.920
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SNP_A-8426515	6	123044547	rs2195686	PKIB	q22.31	0.313	0.218
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SNP_A-8443248	6	123047932	rs7742077	PKIB	q22.31	0.276	0.981
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SNP_A-8413187	6	123065908	rs17084747	PKIB	q22.31	0.082	0.321
SNP_A-8605757	6	123069560	rs9482269	PKIB	q22.31	0.249	0.637
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SNP_A-8689321	6	123088715	rs1132643	PKIB	q22.31	0.369	0.529
SNP_A-8382438	6	136920854	rs9376201	MAP3K5	q23.3	0.149	0.396
SNP_A-8557386	6	136929885	rs13193586	MAP3K5	q23.3	0.076	0.363
SNP_A-2035854	6	136932767	rs9389405	MAP3K5	q23.3	0.155	0.739
SNP_A-1883415	6	136937159	rs2237263	MAP3K5	q23.3	0.149	0.372
SNP_A-8346751	6	136949281	rs9389409	MAP3K5	q23.3	0.157	0.327
SNP_A-8581961	6	136949309	rs9402827	MAP3K5	q23.3	0.153	0.281
SNP_A-8671491	6	136950935	rs2327743	MAP3K5	q23.3	0.172	0.921
SNP_A-1987788	6	136951357	rs760862	MAP3K5	q23.3	0.170	0.811
SNP_A-8671492	6	136951409	rs760863	MAP3K5	q23.3	0.172	0.738
SNP_A-8393818	6	136981511	rs9321564	MAP3K5	q23.3	0.209	0.810
SNP_A-2297858	6	136994623	rs2237268	MAP3K5	q23.3	0.373	0.667
SNP_A-4252549	6	136999357	rs2064205	MAP3K5	q23.3	0.400	0.703
SNP_A-8546991	6	137001971	rs6917580	MAP3K5	q23.3	0.375	0.826
SNP_A-8637302	6	137005186	rs9494547	MAP3K5	q23.3	0.058	0.162
SNP_A-8566105	6	137005747	rs9494549	MAP3K5	q23.3	0.057	0.979
SNP_A-8306367	6	137008312	rs2237269	MAP3K5	q23.3	0.154	0.473
SNP_A-8712155	6	137010234	rs2237271	MAP3K5	q23.3	0.187	0.888
SNP_A-1987789	6	137011307	rs6922031	MAP3K5	q23.3	0.131	0.564
SNP_A-8671493	6	137011546	rs1997703	MAP3K5	q23.3	0.191	0.916
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SNP_A-8566604	6	137019261	rs2076260	MAP3K5	q23.3	0.175	0.161
SNP_A-2109564	6	137020933	rs1011969	MAP3K5	q23.3	0.165	0.734
SNP_A-8686413	6	137034072	rs9376221	MAP3K5	q23.3	0.102	0.846
SNP_A-2307700	6	137036903	rs9402839	MAP3K5	q23.3	0.137	0.845
SNP_A-8570911	6	137059442	rs1009709	MAP3K5	q23.3	0.487	0.313
SNP_A-1987790	6	137069560	rs10484491	MAP3K5	q23.3	0.488	0.956
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SNP_A-2290299	6	137075399	rs911185	MAP3K5	q23.3	0.489	0.926
SNP_A-4293367	6	137083058	rs1028565	MAP3K5	q23.3	0.439	0.804
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SNP_A-1987792	6	137092247	rs9285484	MAP3K5	q23.3	0.450	0.661
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SNP_A-4278163	6	137117703	rs6925103	MAP3K5	q23.3	0.475	0.792
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SNP_A-4212005	6	137120748	rs7739002	MAP3K5	q23.3	0.110	0.184
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SNP_A-8387100	6	137140817	rs11154886	MAP3K5	q23.3	0.406	0.322
SNP_A-1878217	6	137146486	rs9494569	MAP3K5	q23.3	0.360	0.684
SNP_A-1921472	6	137147093	rs9483947	MAP3K5	q23.3	0.361	0.638
SNP_A-8494420	6	137153357	rs4524621	MAP3K5	q23.3	0.358	0.581
SNP_A-8366935	6	161338632	rs625977	MAP3K4	q26	0.176	0.417
SNP_A-8430293	6	161350832	rs676334	MAP3K4	q26	0.072	0.905
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SNP_A-4302400	6	161426929	rs9364586	MAP3K4	q26	0.116	0.919
SNP_A-1799928	6	161428993	rs9355332	MAP3K4	q26	0.113	0.977
SNP_A-1988384	6	161429533	rs1404269	MAP3K4	q26	0.169	0.505
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SNP_A-8703844	6	161446663	rs1534020	MAP3K4	q26	0.170	0.532
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SNP_A-2022921	6	161458240	rs1488	MAP3K4	q26	0.332	0.267
SNP_A-8300675	7	671099	rs7809325	PRKAR1B	p22.3	0.146	0.484
SNP_A-8430489	7	713443	rs4415214	PRKAR1B	p22.3	0.407	0.206
SNP_A-8422201	7	729070	rs4724821	HEATR2	p22.3	0.358	0.761
SNP_A-8516729	7	44259047	rs10232351	CAMK2B	p13	0.408	0.621
SNP_A-8416282	7	44277470	rs10230538	CAMK2B	p13	0.277	0.468
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SNP_A-8326209	7	44286959	rs4724298	CAMK2B	p13	0.183	0.627
SNP_A-8470754	7	44296414	rs10281178	CAMK2B	p13	0.431	0.076
SNP_A-1913700	7	44300378	rs3934888	CAMK2B	p13	0.434	0.150
SNP_A-8490314	7	44301680	rs12216637	CAMK2B	p13	0.114	0.682
SNP_A-1813392	7	44321565	rs4294091	CAMK2B	p13	0.481	0.274
SNP_A-8669774	7	106474152	rs997381	PRKAR2B	q22.3	0.450	0.281
SNP_A-8708698	7	106481048	rs758943	PRKAR2B	q22.3	0.331	0.218
SNP_A-8613466	7	106481602	rs2237650	PRKAR2B	q22.3	0.452	0.819
SNP_A-2169470	7	106506649	rs17340577	PRKAR2B	q22.3	0.089	0.157
SNP_A-4266530	7	106507403	rs2251838	PRKAR2B	q22.3	0.355	0.883
SNP_A-2178086	7	106508168	rs12154324	PRKAR2B	q22.3	0.095	0.231
SNP_A-4216573	7	106517269	rs7786692	PRKAR2B	q22.3	0.096	0.219
SNP_A-4219957	7	106517447	rs17153823	PRKAR2B	q22.3	0.095	0.097
SNP_A-8669775	7	106529284	rs3735613	PRKAR2B	q22.3	0.496	0.746
SNP_A-8331260	7	106549015	rs10281856	PRKAR2B	q22.3	0.399	0.351
SNP_A-2075026	7	106550083	rs10272371	PRKAR2B	q22.3	0.096	0.208
SNP_A-2278737	7	106550454	rs13224682	PRKAR2B	q22.3	0.074	0.329
SNP_A-2137099	7	106550514	rs17425839	PRKAR2B	q22.3	0.093	0.111
SNP_A-1990831	7	106555592	rs9656135	PRKAR2B	q22.3	0.072	0.185
SNP_A-8569085	7	106563803	rs7809330	PRKAR2B	q22.3	0.495	0.714
SNP_A-1802978	7	106564439	rs6960708	PRKAR2B	q22.3	0.099	0.173
SNP_A-8417247	7	106567620	rs3801968	PRKAR2B	q22.3	0.426	0.315
SNP_A-8595189	7	106569919	rs3752645	PRKAR2B	q22.3	0.095	0.097
SNP_A-2138633	7	106575857	rs6946931	PRKAR2B	q22.3	0.187	0.347
SNP_A-1990832	7	106581336	rs1981696	PRKAR2B	q22.3	0.188	0.466
SNP_A-8347862	7	106586279	rs257375	PRKAR2B	q22.3	0.189	0.409
SNP_A-8635523	7	150886109	rs5017428	PRKAG2	q36.1	0.371	0.804
SNP_A-2228406	7	150892423	rs2302533	PRKAG2	q36.1	0.131	0.355
SNP_A-8284975	7	150893238	rs2302532	PRKAG2	q36.1	0.275	0.172

SNP_A-8509984	7	150903423	rs17715595	PRKAG2	q36.1	0.145	0.731
SNP_A-1991757	7	150906739	rs1029946	PRKAG2	q36.1	0.150	0.209
SNP_A-8284976	7	150906805	rs1029945	PRKAG2	q36.1	0.295	0.484
SNP_A-8709655	7	150910802	rs17173199	PRKAG2	q36.1	0.143	0.231
SNP_A-2138366	7	150916094	rs17173202	PRKAG2	q36.1	0.141	0.459
SNP_A-2229375	7	150916125	rs6464148	PRKAG2	q36.1	0.142	0.408
SNP_A-8301438	7	150918894	rs4725411	PRKAG2	q36.1	0.141	0.459
SNP_A-1784479	7	150919943	rs3789813	PRKAG2	q36.1	0.141	0.433
SNP_A-8398409	7	150920999	rs2538036	PRKAG2	q36.1	0.463	0.382
SNP_A-8348140	7	150922510	rs4725413	PRKAG2	q36.1	0.141	0.451
SNP_A-8672858	7	150939500	rs4726060	PRKAG2	q36.1	0.256	0.449
SNP_A-8581772	7	150945458	rs2538045	PRKAG2	q36.1	0.384	0.718
SNP_A-2073394	7	150945706	rs2538042	PRKAG2	q36.1	0.391	0.673
SNP_A-4280215	7	150949911	rs4725415	PRKAG2	q36.1	0.469	0.914
SNP_A-1901852	7	150950488	rs6464156	PRKAG2	q36.1	0.468	0.983
SNP_A-8711360	7	150952094	rs2727565	PRKAG2	q36.1	0.255	0.193
SNP_A-8650995	7	150952256	rs9801653	PRKAG2	q36.1	0.118	0.806
SNP_A-4222472	7	150956126	rs1860736	PRKAG2	q36.1	0.105	0.941
SNP_A-1788050	7	150956192	rs12535806	PRKAG2	q36.1	0.120	0.731
SNP_A-1834698	7	150974571	rs1345278	PRKAG2	q36.1	0.450	0.624
SNP_A-2042599	7	150977323	rs10952315	PRKAG2	q36.1	0.367	0.896
SNP_A-1812832	7	150978395	rs2727527	PRKAG2	q36.1	0.319	0.739
SNP_A-2082185	7	150982545	rs954228	PRKAG2	q36.1	0.289	0.352
SNP_A-8551175	7	150983018	rs2017491	PRKAG2	q36.1	0.329	0.051
SNP_A-8448827	7	150985333	rs1860735	PRKAG2	q36.1	0.103	0.125
SNP_A-2309081	7	150987207	rs2727529	PRKAG2	q36.1	0.392	0.483
SNP_A-1893701	7	150995197	rs1105842	PRKAG2	q36.1	0.157	0.822
SNP_A-1893539	7	150995290	rs1105843	PRKAG2	q36.1	0.314	0.297
SNP_A-1939231	7	150996578	rs954482	PRKAG2	q36.1	0.313	0.204
SNP_A-8501280	7	151005762	rs2727539	PRKAG2	q36.1	0.142	0.145
SNP_A-8647778	7	151013382	rs2727554	PRKAG2	q36.1	0.487	0.206
SNP_A-8697744	7	151013395	rs2727553	PRKAG2	q36.1	0.481	0.160
SNP_A-4290395	7	151015436	rs4726084	PRKAG2	q36.1	0.195	0.548
SNP_A-4247729	7	151018130	rs10277859	PRKAG2	q36.1	0.193	0.801
SNP_A-2085058	7	151018897	rs2024266	PRKAG2	q36.1	0.482	0.246
SNP_A-8537816	7	151019183	rs7797944	PRKAG2	q36.1	0.180	0.406
SNP_A-8324197	7	151019663	rs2727550	PRKAG2	q36.1	0.328	0.790
SNP_A-2231445	7	151020254	rs6970728	PRKAG2	q36.1	0.193	0.786
SNP_A-2036134	7	151020434	rs6970666	PRKAG2	q36.1	0.190	0.871
SNP_A-4245070	7	151022586	rs2727551	PRKAG2	q36.1	0.076	0.369
SNP_A-8477909	7	151026570	rs9648723	PRKAG2	q36.1	0.194	0.298
SNP_A-8304100	7	151033433	rs2727564	PRKAG2	q36.1	0.455	0.074
SNP_A-8651315	7	151033723	rs2374270	PRKAG2	q36.1	0.368	0.487
SNP_A-4284763	7	151034022	rs4725423	PRKAG2	q36.1	0.085	0.187
SNP_A-2187073	7	151034062	rs2727563	PRKAG2	q36.1	0.409	0.598
SNP_A-1887074	7	151036751	rs10480299	PRKAG2	q36.1	0.280	0.128
SNP_A-2111566	7	151045974	rs10224002	PRKAG2	q36.1	0.288	0.108
SNP_A-8404196	7	151053880	rs2536069	PRKAG2	q36.1	0.221	0.252
SNP_A-2202651	7	151054129	rs13239239	PRKAG2	q36.1	0.323	0.844
SNP_A-8304176	7	151061642	rs4726088	PRKAG2	q36.1	0.403	0.194
SNP_A-4281374	7	151062399	rs1108722	PRKAG2	q36.1	0.397	0.930
SNP_A-8418793	7	151067285	rs885273	PRKAG2	q36.1	0.392	0.292
SNP_A-8518567	7	151070761	rs11768438	PRKAG2	q36.1	0.307	0.803
SNP_A-8656895	7	151072903	rs1001117	PRKAG2	q36.1	0.325	0.393
SNP_A-8643885	7	151073677	rs11771330	PRKAG2	q36.1	0.453	0.639
SNP_A-1883435	7	151083561	rs7801616	PRKAG2	q36.1	0.455	0.370
SNP_A-8616844	7	151087015	rs6965771	PRKAG2	q36.1	0.252	0.480
SNP_A-2253591	7	151093470	rs7780008	PRKAG2	q36.1	0.365	0.259
SNP_A-2291492	7	151094097	rs7800069	PRKAG2	q36.1	0.465	0.776
SNP_A-2107674	7	151094445	rs7784818	PRKAG2	q36.1	0.486	0.985
SNP_A-8298079	7	151106857	rs9632641	PRKAG2	q36.1	0.207	0.109
SNP_A-8691676	7	151114829	rs11763144	PRKAG2	q36.1	0.150	0.993
SNP_A-8714213	7	151128901	rs4726097	PRKAG2	q36.1	0.211	0.223
SNP_A-8416447	7	151133235	rs9648724	PRKAG2	q36.1	0.227	0.948
SNP_A-8699658	7	151134234	rs4442045	PRKAG2	q36.1	0.194	0.768
SNP_A-8712371	7	151134743	rs4726100	PRKAG2	q36.1	0.162	0.896
SNP_A-8304248	7	151137088	rs6464173	PRKAG2	q36.1	0.468	0.673
SNP_A-8400235	7	151139190	rs12539356	PRKAG2	q36.1	0.270	0.767
SNP_A-8479991	7	151139777	rs1881638	PRKAG2	q36.1	0.271	0.733
SNP_A-1787510	7	151141292	rs4631369	PRKAG2	q36.1	0.377	0.722
SNP_A-8470174	7	151141463	rs12540943	PRKAG2	q36.1	0.159	0.170
SNP_A-1961623	7	151141504	rs1881634	PRKAG2	q36.1	0.153	0.113
SNP_A-8637726	7	151147753	rs1881629	PRKAG2	q36.1	0.450	0.446
SNP_A-8368707	7	151149683	rs11769593	PRKAG2	q36.1	0.252	0.400

SNP_A-4242522	7	151150061	rs11770376	PRKAG2	q36.1	0.360	0.953
SNP_A-2013017	7	151152511	rs6978617	PRKAG2	q36.1	0.097	0.933
SNP_A-4266687	7	151153648	rs1108845	PRKAG2	q36.1	0.082	0.122
SNP_A-8426165	7	151156399	rs11773373	PRKAG2	q36.1	0.251	0.400
SNP_A-8434452	7	151171892	rs1109277	PRKAG2	q36.1	0.456	0.525
SNP_A-8675572	7	151175924	rs11772236	PRKAG2	q36.1	0.351	0.257
SNP_A-8490884	7	151177522	rs7795096	PRKAG2	q36.1	0.500	0.419
SNP_A-8586815	7	151178940	rs10952322	PRKAG2	q36.1	0.141	0.148
SNP_A-8550960	7	151186459	rs6961830	PRKAG2	q36.1	0.174	0.117
SNP_A-8470212	7	151188347	rs6955784	PRKAG2	q36.1	0.316	0.610
SNP_A-8434380	7	151190466	rs12703164	PRKAG2	q36.1	0.326	0.052
SNP_A-8569100	8	79595987	rs13275966	PKIA	q21.12	0.105	0.944
SNP_A-4213048	8	79613925	rs10504676	PKIA	q21.12	0.108	0.470
SNP_A-2161348	8	79663796	rs16905824	PKIA	q21.12	0.112	0.775
SNP_A-1956412	9	127239694	rs1129	MAPKAP1	q33.3	0.365	0.793
SNP_A-4282148	9	127244580	rs7023669	MAPKAP1	q33.3	0.247	0.329
SNP_A-8599260	9	127248748	rs10760398	MAPKAP1	q33.3	0.322	0.554
SNP_A-4282551	9	127262845	rs7853181	MAPKAP1	q33.3	0.447	0.743
SNP_A-2072855	9	127272220	rs1891034	MAPKAP1	q33.3	0.295	0.831
SNP_A-4202742	9	127290230	rs7046471	MAPKAP1	q33.3	0.314	0.837
SNP_A-2252873	9	127300783	rs7022356	MAPKAP1	q33.3	0.256	0.902
SNP_A-8519067	9	127303238	rs10986778	MAPKAP1	q33.3	0.252	0.779
SNP_A-2026967	9	127315812	rs4837018	MAPKAP1	q33.3	0.464	0.460
SNP_A-8595602	9	127315902	rs4837019	MAPKAP1	q33.3	0.417	0.403
SNP_A-8590962	9	127321243	rs12555339	MAPKAP1	q33.3	0.157	0.800
SNP_A-8589561	9	127328249	rs10120000	MAPKAP1	q33.3	0.361	0.958
SNP_A-2215776	9	127339426	rs522894	MAPKAP1	q33.3	0.170	0.996
SNP_A-2171695	9	127356466	rs829179	MAPKAP1	q33.3	0.084	0.148
SNP_A-2199117	9	127365755	rs530628	MAPKAP1	q33.3	0.471	0.971
SNP_A-1848511	9	127365776	rs494760	MAPKAP1	q33.3	0.057	0.474
SNP_A-8644670	9	127380762	rs12341245	MAPKAP1	q33.3	0.389	0.510
SNP_A-8521766	9	127380844	rs577026	MAPKAP1	q33.3	0.433	0.875
SNP_A-4299286	9	127402558	rs476819	MAPKAP1	q33.3	0.440	0.959
SNP_A-8480814	9	127404722	rs4838276	MAPKAP1	q33.3	0.358	0.603
SNP_A-2061428	9	127409045	rs534214	MAPKAP1	q33.3	0.468	0.822
SNP_A-4241559	9	127417694	rs829312	MAPKAP1	q33.3	0.462	0.553
SNP_A-2152300	9	127434444	rs829311	MAPKAP1	q33.3	0.447	0.771
SNP_A-1811907	9	127447119	rs13300639	MAPKAP1	q33.3	0.385	0.571
SNP_A-2221033	9	127449549	rs13292924	MAPKAP1	q33.3	0.389	0.485
SNP_A-1927284	9	127462849	rs551938	MAPKAP1	q33.3	0.276	0.579
SNP_A-4217995	9	127468088	rs626208	MAPKAP1	q33.3	0.426	0.817
SNP_A-2031839	9	127476230	rs17350527	MAPKAP1	q33.3	0.079	0.920
SNP_A-8390436	9	127477826	rs1250736	MAPKAP1	q33.3	0.438	0.954
SNP_A-4258438	9	127486186	rs4838284	MAPKAP1	q33.3	0.382	0.739
SNP_A-4267739	9	127486709	rs4838285	MAPKAP1	q33.3	0.408	0.709
SNP_A-8559768	9	127488612	rs7862834	MAPKAP1	q33.3	0.135	0.201
SNP_A-8354506	9	127488906	rs7863341	MAPKAP1	q33.3	0.430	1.000
SNP_A-1919232	9	127496460	rs17259739	MAPKAP1	q33.3	0.386	0.528
SNP_A-1864261	10	6509161	rs582052	PRKCQ	p15.1	0.480	0.936
SNP_A-2136491	10	6509330	rs4750439	PRKCQ	p15.1	0.248	0.850
SNP_A-2298977	10	6509679	rs2453	PRKCQ	p15.1	0.240	0.729
SNP_A-2296825	10	6509823	rs2236380	PRKCQ	p15.1	0.279	0.541
SNP_A-8400784	10	6511000	rs17299670	PRKCQ	p15.1	0.095	0.861
SNP_A-1913515	10	6511349	rs681071	PRKCQ	p15.1	0.074	0.839
SNP_A-1869427	10	6511822	rs11596750	PRKCQ	p15.1	0.273	0.444
SNP_A-1867637	10	6512253	rs1889001	PRKCQ	p15.1	0.481	0.681
SNP_A-2239045	10	6512897	rs11258747	PRKCQ	p15.1	0.193	0.075
SNP_A-2241917	10	6514033	rs10796145	PRKCQ	p15.1	0.276	0.704
SNP_A-1847461	10	6517273	rs677986	PRKCQ	p15.1	0.253	0.904
SNP_A-8635664	10	6521233	rs12358161	PRKCQ	p15.1	0.141	0.212
SNP_A-1906357	10	6521410	rs961203	PRKCQ	p15.1	0.058	0.945
SNP_A-8550681	10	6525728	rs7918373	PRKCQ	p15.1	0.107	0.369
SNP_A-8457248	10	6526588	rs17372283	PRKCQ	p15.1	0.196	0.117
SNP_A-8386893	10	6526617	rs624016	PRKCQ	p15.1	0.355	0.838
SNP_A-8488485	10	6527780	rs12573280	PRKCQ	p15.1	0.342	0.851
SNP_A-1993466	10	6537313	rs10508307	PRKCQ	p15.1	0.167	0.214
SNP_A-1993467	10	6537428	rs586457	PRKCQ	p15.1	0.294	0.363
SNP_A-8453799	10	6538729	rs11258943	PRKCQ	p15.1	0.195	0.105
SNP_A-8541749	10	6538805	rs2296123	PRKCQ	p15.1	0.373	0.620
SNP_A-4292124	10	6539234	rs4750491	PRKCQ	p15.1	0.348	0.064
SNP_A-1993470	10	6540724	rs7918923	PRKCQ	p15.1	0.067	0.889
SNP_A-4266973	10	6541194	rs7099451	PRKCQ	p15.1	0.280	0.176
SNP_A-2039362	10	6541451	rs4750495	PRKCQ	p15.1	0.279	0.332
SNP_A-4266974	10	6542103	rs10508308	PRKCQ	p15.1	0.054	0.273

SNP_A-8291581	10	6543456	rs618020	PRKCQ	p15.1	0.104	0.299
SNP_A-1832746	10	6543737	rs4364968	PRKCQ	p15.1	0.374	0.817
SNP_A-1993472	10	6543900	rs12146312	PRKCQ	p15.1	0.271	0.625
SNP_A-8285432	10	6545937	rs3793726	PRKCQ	p15.1	0.065	0.782
SNP_A-8656095	10	6550540	rs7895774	PRKCQ	p15.1	0.295	0.241
SNP_A-2155816	10	6551392	rs591441	PRKCQ	p15.1	0.201	0.787
SNP_A-4266976	10	6560590	rs7083579	PRKCQ	p15.1	0.183	0.866
SNP_A-2259259	10	6561540	rs11259097	PRKCQ	p15.1	0.153	0.267
SNP_A-1865803	10	6562704	rs3793730	PRKCQ	p15.1	0.120	0.478
SNP_A-8529759	10	6562914	rs494800	PRKCQ	p15.1	0.179	0.096
SNP_A-1944680	10	6565959	rs688879	PRKCQ	p15.1	0.400	0.850
SNP_A-1917353	10	6566503	rs501878	PRKCQ	p15.1	0.399	0.747
SNP_A-8348401	10	6567149	rs2236379	PRKCQ	p15.1	0.270	0.847
SNP_A-1825925	10	6567350	rs661891	PRKCQ	p15.1	0.475	0.703
SNP_A-2294075	10	6572010	rs41367851	PRKCQ	p15.1	0.063	0.094
SNP_A-8472588	10	6573883	rs3815975	PRKCQ	p15.1	0.410	0.157
SNP_A-8510994	10	6573906	rs3815974	PRKCQ	p15.1	0.410	0.230
SNP_A-8285440	10	6575438	rs634492	PRKCQ	p15.1	0.358	0.407
SNP_A-2087308	10	6576558	rs6602745	PRKCQ	p15.1	0.103	0.833
SNP_A-1863206	10	6577043	rs11259211	PRKCQ	p15.1	0.109	0.567
SNP_A-4220608	10	6580729	rs650652	PRKCQ	p15.1	0.354	0.235
SNP_A-4274400	10	6585110	rs510745	PRKCQ	p15.1	0.102	0.287
SNP_A-2300959	10	6586077	rs11259272	PRKCQ	p15.1	0.473	0.170
SNP_A-1855073	10	6590205	rs596866	PRKCQ	p15.1	0.185	0.099
SNP_A-8285454	10	6608207	rs4750565	PRKCQ	p15.1	0.123	0.166
SNP_A-1941092	10	6612231	rs11259403	PRKCQ	p15.1	0.352	0.171
SNP_A-2025910	10	6617372	rs12249263	PRKCQ	p15.1	0.257	0.219
SNP_A-2251216	10	6617679	rs11259425	PRKCQ	p15.1	0.134	0.458
SNP_A-1916412	10	6628023	rs10752351	PRKCQ	p15.1	0.181	0.978
SNP_A-2049930	10	6636248	rs6602820	PRKCQ	p15.1	0.452	0.580
SNP_A-1803276	10	6646292	rs4748152	PRKCQ	p15.1	0.148	0.880
SNP_A-8306656	10	6646441	rs943450	PRKCQ	p15.1	0.184	0.248
SNP_A-2122755	10	6648319	rs7072496	PRKCQ	p15.1	0.186	0.334
SNP_A-1890671	10	6648739	rs1887327	PRKCQ	p15.1	0.187	0.239
SNP_A-1938720	10	6651332	rs10906888	PRKCQ	p15.1	0.369	0.938
SNP_A-2087209	10	6654063	rs2387585	PRKCQ	p15.1	0.400	0.872
SNP_A-1993516	10	6656342	rs4620621	PRKCQ	p15.1	0.420	0.716
SNP_A-1993517	10	6656369	rs4750638	PRKCQ	p15.1	0.407	0.791
SNP_A-8627253	10	12433494	rs3013016	CAMK1D	p13	0.406	0.860
SNP_A-8299216	10	12442400	rs7909493	CAMK1D	p13	0.108	0.599
SNP_A-2248691	10	12443034	rs17151584	CAMK1D	p13	0.089	0.294
SNP_A-2073411	10	12452249	rs10906138	CAMK1D	p13	0.243	0.571
SNP_A-1803239	10	12455059	rs41407149	CAMK1D	p13	0.323	0.407
SNP_A-2063826	10	12455154	rs41325747	CAMK1D	p13	0.319	0.354
SNP_A-8565157	10	12458537	rs2724778	CAMK1D	p13	0.187	0.739
SNP_A-1879053	10	12459481	rs12261350	CAMK1D	p13	0.436	0.570
SNP_A-8599945	10	12479829	rs2801490	CAMK1D	p13	0.318	0.946
SNP_A-4272702	10	12485545	rs11257772	CAMK1D	p13	0.098	0.342
SNP_A-2084935	10	12486578	rs1892302	CAMK1D	p13	0.300	0.599
SNP_A-2155105	10	12496489	rs11257778	CAMK1D	p13	0.185	0.424
SNP_A-2298551	10	12498038	rs2399860	CAMK1D	p13	0.184	0.284
SNP_A-1817793	10	12504311	rs10795953	CAMK1D	p13	0.377	0.933
SNP_A-1896138	10	12504501	rs17136824	CAMK1D	p13	0.194	0.113
SNP_A-8471273	10	12504979	rs17136827	CAMK1D	p13	0.196	0.081
SNP_A-8394021	10	12505710	rs11257786	CAMK1D	p13	0.183	0.364
SNP_A-8532351	10	12507234	rs11592149	CAMK1D	p13	0.237	0.293
SNP_A-2048907	10	12508143	rs1111056	CAMK1D	p13	0.437	0.978
SNP_A-2163480	10	12518482	rs11595633	CAMK1D	p13	0.180	0.403
SNP_A-1995546	10	12519661	rs2399858	CAMK1D	p13	0.185	0.199
SNP_A-2053069	10	12520245	rs2768364	CAMK1D	p13	0.184	0.167
SNP_A-1920224	10	12520639	rs2801493	CAMK1D	p13	0.184	0.181
SNP_A-8707317	10	12524562	rs10906150	CAMK1D	p13	0.203	0.906
SNP_A-1840396	10	12527915	rs6602587	CAMK1D	p13	0.358	0.648
SNP_A-8349665	10	12528002	rs6602588	CAMK1D	p13	0.361	0.776
SNP_A-1950697	10	12530792	rs2768451	CAMK1D	p13	0.066	0.264
SNP_A-2150521	10	12530824	rs12763487	CAMK1D	p13	0.220	0.363
SNP_A-2303102	10	12531335	rs11596121	CAMK1D	p13	0.068	0.931
SNP_A-1915883	10	12531353	rs4750216	CAMK1D	p13	0.152	0.714
SNP_A-2134299	10	12533654	rs17569335	CAMK1D	p13	0.295	0.255
SNP_A-1792760	10	12535542	rs11257802	CAMK1D	p13	0.279	0.070
SNP_A-1995553	10	12537753	rs1108131	CAMK1D	p13	0.279	0.023
SNP_A-4267311	10	12537776	rs2768367	CAMK1D	p13	0.128	0.065
SNP_A-8280366	10	12539866	rs2399849	CAMK1D	p13	0.183	0.523
SNP_A-8475107	10	12540181	rs2815613	CAMK1D	p13	0.283	0.925

SNP_A-8456854	10	12544075	rs11257807	CAMK1D	p13	0.167	0.437
SNP_A-8280372	10	12551914	rs7893997	CAMK1D	p13	0.379	0.754
SNP_A-8280791	10	12551939	rs7894008	CAMK1D	p13	0.377	0.598
SNP_A-2234918	10	12555829	rs1543595	CAMK1D	p13	0.228	0.359
SNP_A-8286979	10	12557897	rs4620627	CAMK1D	p13	0.169	0.697
SNP_A-4254260	10	12559076	rs12251472	CAMK1D	p13	0.184	0.651
SNP_A-2183730	10	12559946	rs12780204	CAMK1D	p13	0.192	0.498
SNP_A-2201946	10	12560669	rs12784955	CAMK1D	p13	0.191	0.662
SNP_A-8643472	10	12560721	rs12762343	CAMK1D	p13	0.186	0.524
SNP_A-2055669	10	12563135	rs2768428	CAMK1D	p13	0.238	0.283
SNP_A-8652259	10	12571280	rs11257827	CAMK1D	p13	0.299	0.835
SNP_A-8452614	10	12571625	rs10906157	CAMK1D	p13	0.219	0.722
SNP_A-8609212	10	12573294	rs1998966	CAMK1D	p13	0.255	0.438
SNP_A-8346299	10	12573760	rs2768432	CAMK1D	p13	0.399	0.577
SNP_A-8633091	10	12574304	rs10906158	CAMK1D	p13	0.221	0.154
SNP_A-1925003	10	12575062	rs2768438	CAMK1D	p13	0.319	0.697
SNP_A-2312137	10	12575154	rs2768439	CAMK1D	p13	0.318	0.640
SNP_A-2203283	10	12575203	rs2768440	CAMK1D	p13	0.319	0.713
SNP_A-8478972	10	12577095	rs12248414	CAMK1D	p13	0.223	0.210
SNP_A-8543459	10	12577433	rs17151786	CAMK1D	p13	0.222	0.197
SNP_A-8393572	10	12578296	rs2399846	CAMK1D	p13	0.457	0.584
SNP_A-2099501	10	12578497	rs7078980	CAMK1D	p13	0.217	0.331
SNP_A-2300843	10	12581678	rs7081851	CAMK1D	p13	0.463	0.365
SNP_A-2145383	10	12584244	rs1108959	CAMK1D	p13	0.281	0.563
SNP_A-8602335	10	12584858	rs11257835	CAMK1D	p13	0.056	0.143
SNP_A-1944328	10	12590976	rs11257841	CAMK1D	p13	0.477	0.163
SNP_A-2032149	10	12593004	rs7911448	CAMK1D	p13	0.216	0.637
SNP_A-2166021	10	12594197	rs2815652	CAMK1D	p13	0.454	0.171
SNP_A-2244113	10	12594304	rs41336744	CAMK1D	p13	0.249	0.142
SNP_A-8326627	10	12610518	rs12356332	CAMK1D	p13	0.189	0.770
SNP_A-8395656	10	12612041	rs2815644	CAMK1D	p13	0.376	0.647
SNP_A-2045707	10	12613112	rs2768463	CAMK1D	p13	0.344	0.084
SNP_A-8685188	10	12616011	rs2815641	CAMK1D	p13	0.349	0.912
SNP_A-1878776	10	12617799	rs10458820	CAMK1D	p13	0.282	0.732
SNP_A-1811664	10	12617996	rs6602593	CAMK1D	p13	0.410	0.181
SNP_A-2313545	10	12619465	rs10458822	CAMK1D	p13	0.272	0.402
SNP_A-8581130	10	12620670	rs11257872	CAMK1D	p13	0.259	0.260
SNP_A-8607420	10	12622695	rs7910874	CAMK1D	p13	0.134	0.494
SNP_A-8534321	10	12622719	rs11257877	CAMK1D	p13	0.260	0.272
SNP_A-8367068	10	12622790	rs2815638	CAMK1D	p13	0.399	0.423
SNP_A-8605157	10	12623259	rs1126368	CAMK1D	p13	0.107	0.036
SNP_A-8628383	10	12623318	rs2492953	CAMK1D	p13	0.095	0.110
SNP_A-2073968	10	12624519	rs2815637	CAMK1D	p13	0.353	0.496
SNP_A-2182648	10	12626943	rs17493316	CAMK1D	p13	0.315	0.790
SNP_A-1874751	10	12629156	rs7078960	CAMK1D	p13	0.335	0.715
SNP_A-8356130	10	12631718	rs7897059	CAMK1D	p13	0.410	0.707
SNP_A-8633232	10	12634527	rs2815630	CAMK1D	p13	0.156	0.352
SNP_A-8604749	10	12637439	rs2815628	CAMK1D	p13	0.309	0.023
SNP_A-8452776	10	12637464	rs10906166	CAMK1D	p13	0.372	0.449
SNP_A-8520982	10	12637496	rs2815627	CAMK1D	p13	0.308	0.017
SNP_A-2000970	10	12639700	rs2815624	CAMK1D	p13	0.121	0.698
SNP_A-4268196	10	12640070	rs2815623	CAMK1D	p13	0.059	0.543
SNP_A-2046458	10	12640674	rs2768348	CAMK1D	p13	0.310	0.035
SNP_A-4255641	10	12641445	rs2648708	CAMK1D	p13	0.117	0.848
SNP_A-1874304	10	12641479	rs12773063	CAMK1D	p13	0.426	0.045
SNP_A-8657116	10	12641510	rs11257888	CAMK1D	p13	0.427	0.039
SNP_A-4223263	10	12643507	rs12764138	CAMK1D	p13	0.425	0.109
SNP_A-4302372	10	12644337	rs2815617	CAMK1D	p13	0.310	0.047
SNP_A-1809832	10	12644480	rs2768352	CAMK1D	p13	0.271	0.051
SNP_A-2181106	10	12646058	rs11257892	CAMK1D	p13	0.061	0.607
SNP_A-2312652	10	12646287	rs7896236	CAMK1D	p13	0.470	0.943
SNP_A-8280824	10	12648682	rs1409961	CAMK1D	p13	0.466	0.811
SNP_A-8367998	10	12652344	rs12572894	CAMK1D	p13	0.178	0.075
SNP_A-8443225	10	12656239	rs2815615	CAMK1D	p13	0.396	0.021
SNP_A-2100726	10	12668507	rs4364954	CAMK1D	p13	0.317	0.035
SNP_A-8471113	10	12669374	rs2895534	CAMK1D	p13	0.194	0.548
SNP_A-1949610	10	12672162	rs2399880	CAMK1D	p13	0.137	0.601
SNP_A-2181586	10	12673372	rs10732936	CAMK1D	p13	0.321	0.027
SNP_A-8332150	10	12678891	rs10906180	CAMK1D	p13	0.447	0.181
SNP_A-2224069	10	12680803	rs7911208	CAMK1D	p13	0.270	0.302
SNP_A-8621541	10	12681466	rs10795966	CAMK1D	p13	0.309	0.371
SNP_A-8293473	10	12685143	rs10906182	CAMK1D	p13	0.082	0.967
SNP_A-1933307	10	12685893	rs11596728	CAMK1D	p13	0.286	0.159
SNP_A-2237869	10	12686538	rs7906212	CAMK1D	p13	0.083	0.087

SNP_A-8491054	10	12686819	rs17151970	CAMK1D	p13	0.142	0.262
SNP_A-1870292	10	12688155	rs17151973	CAMK1D	p13	0.262	0.366
SNP_A-8377666	10	12690925	rs12414714	CAMK1D	p13	0.101	0.149
SNP_A-2247873	10	12695806	rs879753	CAMK1D	p13	0.268	0.511
SNP_A-4234545	10	12698876	rs17152001	CAMK1D	p13	0.070	0.536
SNP_A-1807273	10	12698895	rs7912882	CAMK1D	p13	0.423	0.154
SNP_A-8390763	10	12700517	rs11257918	CAMK1D	p13	0.259	0.834
SNP_A-2241975	10	12709055	rs11257922	CAMK1D	p13	0.490	0.975
SNP_A-2127934	10	12709525	rs11595663	CAMK1D	p13	0.264	0.918
SNP_A-8562082	10	12717620	rs17152037	CAMK1D	p13	0.300	0.607
SNP_A-8286980	10	12721626	rs6602603	CAMK1D	p13	0.405	0.897
SNP_A-8318937	10	12722851	rs10450540	CAMK1D	p13	0.287	0.860
SNP_A-8344907	10	12731061	rs7921813	CAMK1D	p13	0.116	0.771
SNP_A-8653506	10	12731450	rs12248346	CAMK1D	p13	0.279	0.976
SNP_A-8412541	10	12731582	rs17495691	CAMK1D	p13	0.120	0.660
SNP_A-8410169	10	12735393	rs7071404	CAMK1D	p13	0.345	0.624
SNP_A-8595078	10	12736126	rs11257930	CAMK1D	p13	0.477	0.234
SNP_A-8641387	10	12736967	rs4750247	CAMK1D	p13	0.330	0.426
SNP_A-2121832	10	12739541	rs7905330	CAMK1D	p13	0.458	0.433
SNP_A-8423981	10	12741948	rs11257932	CAMK1D	p13	0.120	0.229
SNP_A-2286665	10	12744197	rs10752271	CAMK1D	p13	0.088	0.161
SNP_A-2000973	10	12746743	rs4417163	CAMK1D	p13	0.452	0.098
SNP_A-2100883	10	12747804	rs10906199	CAMK1D	p13	0.211	0.544
SNP_A-4286379	10	12749730	rs7091959	CAMK1D	p13	0.347	0.904
SNP_A-8498736	10	12757339	rs10795975	CAMK1D	p13	0.466	0.105
SNP_A-8555611	10	12760690	rs4747996	CAMK1D	p13	0.346	0.841
SNP_A-2046604	10	12761513	rs7893280	CAMK1D	p13	0.089	0.152
SNP_A-1995627	10	12762565	rs10508446	CAMK1D	p13	0.346	0.724
SNP_A-8482203	10	12764818	rs4520494	CAMK1D	p13	0.351	0.451
SNP_A-8451250	10	12766067	rs2895526	CAMK1D	p13	0.456	0.159
SNP_A-1995628	10	12783648	rs2399864	CAMK1D	p13	0.373	0.951
SNP_A-1913139	10	12784342	rs4623785	CAMK1D	p13	0.053	0.812
SNP_A-8465069	10	12787534	rs4237425	CAMK1D	p13	0.346	0.736
SNP_A-8430451	10	12787678	rs11257948	CAMK1D	p13	0.304	0.352
SNP_A-8415106	10	12788822	rs4750249	CAMK1D	p13	0.227	0.816
SNP_A-8446711	10	12801690	rs7923465	CAMK1D	p13	0.483	0.232
SNP_A-4267327	10	12802309	rs723211	CAMK1D	p13	0.486	0.388
SNP_A-1995632	10	12802482	rs723210	CAMK1D	p13	0.488	0.412
SNP_A-4245317	10	12811686	rs7077423	CAMK1D	p13	0.319	0.709
SNP_A-2000974	10	12818978	rs4750253	CAMK1D	p13	0.443	0.872
SNP_A-4213319	10	12832547	rs17152197	CAMK1D	p13	0.175	0.575
SNP_A-8381455	10	12833952	rs11596618	CAMK1D	p13	0.138	0.274
SNP_A-4229534	10	12834342	rs17152205	CAMK1D	p13	0.172	0.378
SNP_A-8632789	10	12837291	rs10906218	CAMK1D	p13	0.131	0.396
SNP_A-8281253	10	12837764	rs4132050	CAMK1D	p13	0.338	0.645
SNP_A-1995641	10	12837834	rs41380844	CAMK1D	p13	0.206	0.450
SNP_A-8286981	10	12837860	rs4132049	CAMK1D	p13	0.281	0.329
SNP_A-1828085	10	12838603	rs4078402	CAMK1D	p13	0.363	0.346
SNP_A-2071684	10	12840721	rs10752275	CAMK1D	p13	0.102	0.467
SNP_A-8348419	10	12841507	rs2989500	CAMK1D	p13	0.371	0.844
SNP_A-1897320	10	12844670	rs11257974	CAMK1D	p13	0.111	0.349
SNP_A-2304748	10	12845297	rs3802573	CAMK1D	p13	0.110	0.533
SNP_A-4268197	10	12845383	rs3802572	CAMK1D	p13	0.494	0.445
SNP_A-2000976	10	12845436	rs3802570	CAMK1D	p13	0.335	0.535
SNP_A-8312142	10	12849037	rs11257979	CAMK1D	p13	0.072	0.905
SNP_A-1944793	10	12849657	rs7910587	CAMK1D	p13	0.216	0.097
SNP_A-8333183	10	12850576	rs2482052	CAMK1D	p13	0.204	0.436
SNP_A-1898790	10	12854906	rs3781076	CAMK1D	p13	0.117	0.333
SNP_A-8554443	10	12854934	rs2493775	CAMK1D	p13	0.208	0.550
SNP_A-8346697	10	12859895	rs4750258	CAMK1D	p13	0.286	0.505
SNP_A-2057033	10	12860217	rs3802569	CAMK1D	p13	0.223	0.682
SNP_A-1847369	10	12866039	rs3802560	CAMK1D	p13	0.222	0.711
SNP_A-2200877	10	12868296	rs10906223	CAMK1D	p13	0.217	0.958
SNP_A-2033615	10	12868459	rs914328	CAMK1D	p13	0.217	0.958
SNP_A-8653306	10	12870975	rs12359004	CAMK1D	p13	0.053	0.161
SNP_A-8328214	10	12871675	rs12767282	CAMK1D	p13	0.166	0.708
SNP_A-1931100	10	12872599	rs4747999	CAMK1D	p13	0.427	0.867
SNP_A-8534490	10	12873618	rs11257991	CAMK1D	p13	0.099	0.343
SNP_A-8281277	10	12874932	rs928336	CAMK1D	p13	0.444	0.784
SNP_A-1995659	10	12875051	rs928337	CAMK1D	p13	0.393	0.524
SNP_A-1995661	10	12875594	rs2493766	CAMK1D	p13	0.375	0.573
SNP_A-8693709	10	12875731	rs11596463	CAMK1D	p13	0.328	0.322
SNP_A-1876279	10	12876178	rs10906224	CAMK1D	p13	0.333	0.398
SNP_A-1995662	10	12876488	rs17152268	CAMK1D	p13	0.073	0.176

SNP_A-8281665	10	12876558	rs1929389	CAMK1D	p13	0.447	0.743
SNP_A-8281666	10	12876607	rs1929388	CAMK1D	p13	0.418	0.747
SNP_A-4213320	10	12876845	rs1929383	CAMK1D	p13	0.418	0.821
SNP_A-4233438	10	12877448	rs34278684	CAMK1D	p13	0.069	0.069
SNP_A-1936417	10	12880848	rs1556408	CAMK1D	p13	0.375	0.695
SNP_A-1899081	10	12882185	rs41402449	CAMK1D	p13	0.060	0.114
SNP_A-1806035	10	12887844	rs4750267	CAMK1D	p13	0.387	0.396
SNP_A-8584436	10	12888039	rs17136885	CAMK1D	p13	0.083	0.229
SNP_A-8488232	10	12890242	rs1999369	CAMK1D	p13	0.088	0.272
SNP_A-2111454	10	12890474	rs10906229	CAMK1D	p13	0.364	0.377
SNP_A-8659980	10	12891662	rs12358381	CAMK1D	p13	0.279	0.034
SNP_A-2195214	10	12895162	rs11258009	CAMK1D	p13	0.106	0.192
SNP_A-8700699	10	12901951	rs1630635	CAMK1D	p13	0.086	0.430
SNP_A-2227562	10	12902342	rs1627294	CAMK1D	p13	0.207	0.564
SNP_A-2179057	10	12904316	rs1644428	CAMK1D	p13	0.289	0.605
SNP_A-8648723	10	12904400	rs1757052	CAMK1D	p13	0.289	0.916
SNP_A-8331063	10	12907604	rs1757051	CAMK1D	p13	0.253	0.440
SNP_A-2059103	10	12908310	rs1644391	CAMK1D	p13	0.293	0.730
SNP_A-2124948	10	30771645	rs8176983	MAP3K8	p11.23	0.092	0.577
SNP_A-1805768	10	30771666	rs8176984	MAP3K8	p11.23	0.092	0.898
SNP_A-1908602	10	30774889	rs598009	MAP3K8	p11.23	0.214	0.083
SNP_A-2243084	10	30779064	rs303428	MAP3K8	p11.23	0.382	0.063
SNP_A-8290587	10	30780385	rs303426	MAP3K8	p11.23	0.378	0.092
SNP_A-1924274	10	30784089	rs650788	MAP3K8	p11.23	0.138	0.119
SNP_A-2175385	10	30788504	rs8177029	MAP3K8	p11.23	0.108	0.944
SNP_A-2136321	10	49197212	rs7068398	MAPK8	q11.22	0.211	0.906
SNP_A-2000433	10	49217160	rs1112268	MAPK8	q11.22	0.214	0.665
SNP_A-4222841	10	49220700	rs6537561	MAPK8	q11.22	0.428	0.941
SNP_A-4220841	10	49235992	rs2590391	MAPK8	q11.22	0.214	0.521
SNP_A-2257035	10	49239736	rs17697885	MAPK8	q11.22	0.098	0.627
SNP_A-4283442	10	49246884	rs1881735	MAPK8	q11.22	0.214	0.696
SNP_A-2163878	10	49261724	rs2698761	MAPK8	q11.22	0.429	0.885
SNP_A-4272127	10	49262758	rs17010430	MAPK8	q11.22	0.055	0.385
SNP_A-1781918	10	49264246	rs10857560	MAPK8	q11.22	0.432	0.760
SNP_A-1816092	10	49265870	rs17697960	MAPK8	q11.22	0.111	0.569
SNP_A-8497559	10	49275145	rs2440861	MAPK8	q11.22	0.312	0.959
SNP_A-8675548	10	49278796	rs17697978	MAPK8	q11.22	0.062	0.679
SNP_A-2146965	10	49279184	rs17698002	MAPK8	q11.22	0.061	0.642
SNP_A-4248684	10	49290273	rs9888128	MAPK8	q11.22	0.427	0.867
SNP_A-8329336	10	49297918	rs2289805	MAPK8	q11.22	0.162	0.925
SNP_A-2000441	10	49312152	rs11101320	MAPK8	q11.22	0.425	0.688
SNP_A-2000443	10	49312216	rs7086275	MAPK8	q11.22	0.425	0.681
SNP_A-1789847	10	75247849	rs7080350	CAMK2G	q22.2	0.433	0.233
SNP_A-2044332	10	75287350	rs2664280	CAMK2G	q22.2	0.476	0.642
SNP_A-2176677	10	75302766	rs2675671	CAMK2G	q22.2	0.472	0.625
SNP_A-8327814	11	65124899	rs10791821	MAP3K11	q13.1	0.252	0.810
SNP_A-2011704	11	65128180	rs1151488	MAP3K11	q13.1	0.296	0.375
SNP_A-8461425	11	65129094	rs7116712	MAP3K11	q13.1	0.428	0.443
SNP_A-8708739	12	52166920	rs7958457	MAP3K12	q13.13	0.119	0.921
SNP_A-4272432	12	110765396	rs4767068	MAPKAPK5	q24.12	0.182	0.380
SNP_A-8385458	12	110769925	rs4346023	MAPKAPK5	q24.12	0.292	0.943
SNP_A-8459039	12	110807399	rs12315146	MAPKAPK5	q24.13	0.092	0.387
SNP_A-4219242	12	110809229	rs12423041	MAPKAPK5	q24.13	0.157	0.808
SNP_A-1892912	12	110811440	rs16941724	MAPKAPK5	q24.13	0.067	0.252
SNP_A-2270138	12	118590759	rs6490267	PRKAB1	q24.23	0.329	0.731
SNP_A-4303936	12	118600877	rs278151	PRKAB1	q24.23	0.312	0.877
SNP_A-8478035	12	118603566	rs4213	PRKAB1	q24.23	0.311	0.831
SNP_A-8374131	12	120164843	rs11065504	CAMKK2	q24.31	0.344	0.281
SNP_A-8695002	12	120165521	rs1653591	CAMKK2	q24.31	0.221	0.148
SNP_A-2062663	12	120165919	rs1140886	CAMKK2	q24.31	0.278	0.565
SNP_A-2201096	12	120166070	rs1063843	CAMKK2	q24.31	0.222	0.135
SNP_A-2167062	12	120169571	rs2686342	CAMKK2	q24.31	0.222	0.193
SNP_A-8437553	12	120170167	rs3794208	CAMKK2	q24.31	0.129	0.656
SNP_A-2113248	12	120171857	rs2288693	CAMKK2	q24.31	0.050	0.225
SNP_A-8330751	12	120179905	rs2686346	CAMKK2	q24.31	0.463	0.447
SNP_A-8332641	12	120192654	rs1718123	CAMKK2	q24.31	0.498	0.212
SNP_A-4257403	12	120199778	rs9805130	CAMKK2	q24.31	0.411	0.271
SNP_A-8353111	14	50008958	rs4898658	MAP4K5	q22.1	0.075	0.512
SNP_A-4260067	14	50017222	rs11157745	MAP4K5	q22.1	0.088	0.687
SNP_A-2092571	14	50038960	rs2180499	MAP4K5	q22.1	0.053	0.566
SNP_A-4282792	14	50039198	rs2144975	MAP4K5	q22.1	0.052	0.589
SNP_A-8498776	14	50043382	rs17718580	MAP4K5	q22.1	0.094	0.091
SNP_A-8388911	14	50058668	rs12882884	MAP4K5	q22.1	0.137	0.820
SNP_A-4297690	14	50062686	rs7160618	MAP4K5	q22.1	0.073	0.448

SNP_A-1874459	14	54599873	rs3742564	MAPK1IP1L	q22.3	0.357	0.739
SNP_A-1911919	14	54606159	rs17128145	MAPK1IP1L	q22.3	0.350	0.761
SNP_A-1931984	14	60859258	rs4902046	PRKCH	q23.1	0.063	0.319
SNP_A-8636880	14	60860747	rs8017122	PRKCH	q23.1	0.086	0.442
SNP_A-8713785	14	60868578	rs12101174	PRKCH	q23.1	0.074	0.166
SNP_A-4294311	14	60883016	rs1957902	PRKCH	q23.1	0.301	0.682
SNP_A-8529720	14	60885908	rs6573381	PRKCH	q23.1	0.088	0.060
SNP_A-8463426	14	60886593	rs1033910	PRKCH	q23.1	0.271	0.919
SNP_A-1829740	14	60887286	rs2181987	PRKCH	q23.1	0.084	0.215
SNP_A-8535987	14	60888413	rs8012072	PRKCH	q23.1	0.178	0.672
SNP_A-8672839	14	60895660	rs12437249	PRKCH	q23.1	0.264	0.525
SNP_A-2159814	14	60897022	rs6573385	PRKCH	q23.1	0.083	0.083
SNP_A-2288081	14	60901613	rs17098278	PRKCH	q23.1	0.112	0.133
SNP_A-1906709	14	60901663	rs17098279	PRKCH	q23.1	0.054	0.521
SNP_A-8324232	14	60909131	rs8009446	PRKCH	q23.1	0.100	0.584
SNP_A-8511480	14	60915883	rs10149384	PRKCH	q23.1	0.145	0.318
SNP_A-8472809	14	60922546	rs1886467	PRKCH	q23.1	0.158	0.192
SNP_A-4240469	14	60922603	rs12100914	PRKCH	q23.1	0.103	0.523
SNP_A-8294325	14	60923549	rs4902052	PRKCH	q23.1	0.223	0.116
SNP_A-2298831	14	60929984	rs1957907	PRKCH	q23.1	0.071	0.938
SNP_A-8540419	14	60931057	rs1957910	PRKCH	q23.1	0.070	0.562
SNP_A-8439856	14	60935032	rs1957912	PRKCH	q23.1	0.380	0.913
SNP_A-8701557	14	60936263	rs12887002	PRKCH	q23.1	0.306	0.512
SNP_A-8409595	14	60944127	rs767757	PRKCH	q23.1	0.386	0.645
SNP_A-1937739	14	60944201	rs767755	PRKCH	q23.1	0.322	0.956
SNP_A-8459867	14	60946310	rs10149839	PRKCH	q23.1	0.311	0.898
SNP_A-8301275	14	60949570	rs12892443	PRKCH	q23.1	0.287	0.590
SNP_A-4249665	14	60950281	rs1536014	PRKCH	q23.1	0.094	0.033
SNP_A-8615384	14	60952025	rs1570718	PRKCH	q23.1	0.229	0.960
SNP_A-8612050	14	60955193	rs4605077	PRKCH	q23.1	0.178	0.690
SNP_A-8486057	14	60955610	rs11627158	PRKCH	q23.1	0.178	0.690
SNP_A-2089042	14	60956159	rs7155214	PRKCH	q23.1	0.177	0.653
SNP_A-8299147	14	60956523	rs12590425	PRKCH	q23.1	0.272	0.204
SNP_A-8612265	14	60957230	rs11852192	PRKCH	q23.1	0.094	0.028
SNP_A-8712360	14	60959051	rs17098343	PRKCH	q23.1	0.378	0.635
SNP_A-2301229	14	60959560	rs11627926	PRKCH	q23.1	0.258	0.151
SNP_A-2238813	14	60962944	rs11621346	PRKCH	q23.1	0.229	0.581
SNP_A-1788892	14	60968333	rs17098351	PRKCH	q23.1	0.294	0.908
SNP_A-2039744	14	60968592	rs17098356	PRKCH	q23.1	0.281	0.704
SNP_A-2129880	14	60969235	rs12590817	PRKCH	q23.1	0.203	0.912
SNP_A-8641436	14	60986931	rs2296274	PRKCH	q23.1	0.230	0.417
SNP_A-8651310	14	60997338	rs8010084	PRKCH	q23.1	0.070	0.238
SNP_A-4240499	14	61003289	rs912617	PRKCH	q23.1	0.078	0.504
SNP_A-2267277	14	61004561	rs8019776	PRKCH	q23.1	0.050	0.641
SNP_A-2003779	14	61005927	rs8011286	PRKCH	q23.1	0.055	0.920
SNP_A-8641445	14	61006917	rs3783787	PRKCH	q23.1	0.269	0.957
SNP_A-4280842	14	61006977	rs3783786	PRKCH	q23.1	0.223	0.934
SNP_A-4294328	14	61007554	rs10483734	PRKCH	q23.1	0.060	0.577
SNP_A-8641448	14	61007908	rs4899049	PRKCH	q23.1	0.057	0.989
SNP_A-1793744	14	61009324	rs11621877	PRKCH	q23.1	0.270	0.314
SNP_A-8462185	14	61010663	rs2181985	PRKCH	q23.1	0.275	0.310
SNP_A-8312482	14	61010694	rs2147539	PRKCH	q23.1	0.349	0.495
SNP_A-1951245	14	61013639	rs4899050	PRKCH	q23.1	0.236	0.315
SNP_A-8532254	14	61014635	rs1886461	PRKCH	q23.1	0.286	0.505
SNP_A-2138779	14	61014730	rs1886462	PRKCH	q23.1	0.089	0.294
SNP_A-2223822	14	61017755	rs8008798	PRKCH	q23.1	0.142	0.408
SNP_A-8642218	14	61018804	rs1886464	PRKCH	q23.1	0.151	0.574
SNP_A-2250360	14	61022592	rs17098514	PRKCH	q23.1	0.062	0.677
SNP_A-8716034	14	61022928	rs3783770	PRKCH	q23.1	0.104	0.459
SNP_A-8642254	14	61026577	rs4902064	PRKCH	q23.1	0.173	0.901
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SNP_A-4282562	14	61028043	rs17098542	PRKCH	q23.1	0.132	0.539
SNP_A-8545275	14	61030659	rs12433533	PRKCH	q23.1	0.137	0.387
SNP_A-8677144	14	61030926	rs12437374	PRKCH	q23.1	0.111	0.516
SNP_A-2200645	14	61031163	rs12897140	PRKCH	q23.1	0.132	0.691
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SNP_A-8373742	14	61045858	rs1088681	PRKCH	q23.1	0.151	0.556
SNP_A-8462507	14	61048031	rs1091679	PRKCH	q23.1	0.166	0.555
SNP_A-8469231	14	61050277	rs2249032	PRKCH	q23.1	0.096	0.448
SNP_A-8642978	14	61051517	rs3783759	PRKCH	q23.1	0.212	0.200
SNP_A-8482974	14	61053696	rs3751289	PRKCH	q23.1	0.199	0.671
SNP_A-2273834	14	61054437	rs2252267	PRKCH	q23.1	0.281	0.311
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SNP_A-8642997	14	61059814	rs12586812	PRKCH	q23.1	0.221	0.368
SNP_A-4233844	14	61060072	rs10483742	PRKCH	q23.1	0.105	0.941
SNP_A-1898268	14	61060614	rs12883769	PRKCH	q23.1	0.078	0.911
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SNP_A-2166272	14	61068370	rs2184634	PRKCH	q23.1	0.107	0.945
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SNP_A-8650239	14	61079990	rs3783754	PRKCH	q23.1	0.110	0.298
SNP_A-2223910	14	61080552	rs10483743	PRKCH	q23.1	0.069	0.211
SNP_A-8367118	14	61083587	rs10138449	PRKCH	q23.1	0.109	0.573
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SNP_A-2003824	14	70270685	rs6573978	MAP3K9	q24.2	0.098	0.344
SNP_A-2248156	14	70271557	rs4899367	MAP3K9	q24.2	0.067	0.154
SNP_A-4297560	14	70272403	rs4141095	MAP3K9	q24.2	0.099	0.371
SNP_A-8356985	14	70274122	rs8011047	MAP3K9	q24.2	0.128	0.489
SNP_A-4295038	14	70281911	rs10483834	MAP3K9	q24.2	0.262	0.430
SNP_A-8638760	14	70282567	rs2269946	MAP3K9	q24.2	0.052	0.174
SNP_A-2208009	14	70285133	rs2332457	MAP3K9	q24.2	0.426	0.224
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SNP_A-2130417	14	70297666	rs3814872	MAP3K9	q24.2	0.109	0.473
SNP_A-2065586	14	70298454	rs9323548	MAP3K9	q24.2	0.296	0.437
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SNP_A-8655808	14	70325659	rs11626707	MAP3K9	q24.2	0.475	0.431
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SNP_A-1845711	14	70344332	rs10873243	MAP3K9	q24.2	0.301	0.442
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SNP_A-8690902	14	70344475	rs11158882	MAP3K9	q24.2	0.303	0.423
SNP_A-2274082	15	39859915	rs1106934	MAPKBP1	q15.1	0.162	0.518
SNP_A-1906143	15	39878504	rs2925339	MAPKBP1	q15.1	0.322	0.156
SNP_A-2085945	15	39878677	rs1197671	MAPKBP1	q15.1	0.305	0.370
SNP_A-8522318	15	39888986	rs16972089	MAPKBP1	q15.1	0.165	0.158
SNP_A-8311348	15	39889577	rs12440605	MAPKBP1	q15.1	0.484	0.957
SNP_A-8306551	15	50106988	rs11636443	MAPK6	q21.2	0.431	0.159
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SNP_A-1952547	15	64470005	rs12899337	MAP2K1	q22.31	0.078	0.911
SNP_A-1925869	15	64473824	rs16953563	MAP2K1	q22.31	0.271	0.378
SNP_A-8713578	15	64481485	rs16949879	MAP2K1	q22.31	0.311	0.713
SNP_A-1852767	15	64491503	rs2053005	MAP2K1	q22.31	0.079	0.690
SNP_A-8501008	15	64493559	rs12909274	MAP2K1	q22.31	0.154	0.620
SNP_A-1867883	15	64496440	rs7168238	MAP2K1	q22.31	0.080	0.982
SNP_A-8588910	15	64506335	rs1432441	MAP2K1	q22.31	0.309	0.860
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SNP_A-1914187	15	64512399	rs11632225	MAP2K1	q22.31	0.153	0.858
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SNP_A-8475137	15	64518339	rs8036023	MAP2K1	q22.31	0.311	0.493
SNP_A-8440548	15	64528441	rs11629783	MAP2K1	q22.31	0.246	0.348
SNP_A-1814659	15	64556238	rs4075665	MAP2K1	q22.31	0.080	0.982

SNP_A-2148826	15	64559061	rs4255740	MAP2K1	q22.31	0.307	0.661
SNP_A-8697907	15	64560787	rs11071894	MAP2K1	q22.31	0.087	0.248
SNP_A-1801907	15	64561613	rs11634062	MAP2K1	q22.31	0.150	0.789
SNP_A-8551688	15	64563494	rs12594592	MAP2K1	q22.31	0.149	0.374
SNP_A-1935747	15	65624462	rs2583587	MAP2K5	q23	0.235	0.129
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SNP_A-4286893	15	65668983	rs6494673	MAP2K5	q23	0.086	0.813
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SNP_A-4239542	15	65673405	rs10851775	MAP2K5	q23	0.084	0.842
SNP_A-8312471	15	65679820	rs3865018	MAP2K5	q23	0.280	0.764
SNP_A-8421418	15	65679846	rs17241808	MAP2K5	q23	0.467	0.327
SNP_A-1920885	15	65687522	rs1878700	MAP2K5	q23	0.091	0.939
SNP_A-2298097	15	65687937	rs1878699	MAP2K5	q23	0.395	0.943
SNP_A-4221018	15	65688586	rs12593494	MAP2K5	q23	0.240	0.104
SNP_A-8710024	15	65692960	rs11631249	MAP2K5	q23	0.149	0.102
SNP_A-8417413	15	65696333	rs12902812	MAP2K5	q23	0.280	0.745
SNP_A-2256338	15	65701806	rs2899728	MAP2K5	q23	0.085	0.748
SNP_A-8344362	15	65708228	rs8025889	LOC728643	q23	0.465	1.000
SNP_A-8637497	15	65721221	rs11631474	MAP2K5	q23	0.469	0.671
SNP_A-2228598	15	65738204	rs12438118	MAP2K5	q23	0.268	0.786
SNP_A-4224043	15	65739445	rs7170841	MAP2K5	q23	0.168	0.885
SNP_A-8422674	15	65739976	rs938875	MAP2K5	q23	0.457	0.763
SNP_A-2123861	15	65746518	rs8032675	MAP2K5	q23	0.458	0.815
SNP_A-1823224	15	65768232	rs16951125	MAP2K5	q23	0.085	0.201
SNP_A-2060485	15	65771759	rs4343227	MAP2K5	q23	0.171	0.998
SNP_A-2127307	15	65774855	rs4331293	MAP2K5	q23	0.288	0.778
SNP_A-8658737	15	65789656	rs3784695	MAP2K5	q23	0.481	0.484
SNP_A-4239546	15	65796629	rs6494691	MAP2K5	q23	0.184	0.707
SNP_A-2293047	15	65801304	rs10518738	MAP2K5	q23	0.170	0.996
SNP_A-8711200	15	65802025	rs10518739	MAP2K5	q23	0.451	0.779
SNP_A-8711202	15	65802293	rs11639267	MAP2K5	q23	0.171	0.851
SNP_A-2293054	15	65806172	rs10518740	MAP2K5	q23	0.091	0.971
SNP_A-8645513	15	65816234	rs3784705	MAP2K5	q23	0.169	0.925
SNP_A-1921942	15	65823906	rs12593813	MAP2K5	q23	0.354	0.927
SNP_A-4254017	15	65824632	rs11635424	MAP2K5	q23	0.354	0.927
SNP_A-8494788	15	65827320	rs12592315	MAP2K5	q23	0.496	0.686
SNP_A-1930409	15	65834069	rs16951231	MAP2K5	q23	0.095	0.473
SNP_A-8512670	15	65837831	rs7183639	MAP2K5	q23	0.097	0.400
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SNP_A-1957605	15	65842050	rs868037	MAP2K5	q23	0.352	0.968
SNP_A-2081211	15	65845033	rs17244146	MAP2K5	q23	0.092	0.905
SNP_A-1811749	15	65845701	rs11071957	MAP2K5	q23	0.239	0.932
SNP_A-8399897	15	65845957	rs11071959	MAP2K5	q23	0.242	0.981
SNP_A-8711233	15	65850029	rs10518744	MAP2K5	q23	0.105	0.101
SNP_A-8711235	15	65851299	rs16951256	MAP2K5	q23	0.096	0.445
SNP_A-8711241	15	65857673	rs4539549	MAP2K5	q23	0.408	0.561
SNP_A-2026619	15	65859129	rs4489954	MAP2K5	q23	0.333	0.716
SNP_A-2298200	15	65859329	rs3784709	MAP2K5	q23	0.353	0.711
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SNP_A-8478894	15	65859581	rs3784711	MAP2K5	q23	0.402	0.607
SNP_A-2298955	15	65865472	rs4451902	MAP2K5	q23	0.146	0.773
SNP_A-1853662	15	65866142	rs12593640	MAP2K5	q23	0.091	0.572
SNP_A-4239548	15	65866615	rs12593698	MAP2K5	q23	0.094	0.497
SNP_A-8442634	15	65875958	rs12905175	MAP2K5	q23	0.050	0.705
SNP_A-2210511	15	65877754	rs11856999	MAP2K5	q23	0.147	0.159
SNP_A-2293119	15	65877878	rs2127162	MAP2K5	q23	0.498	0.747
SNP_A-2040764	15	65882139	rs1026732	MAP2K5	q23	0.351	0.940
SNP_A-8366379	16	1699795	rs17135499	MAPK8IP3	p13.3	0.082	0.915
SNP_A-8711954	16	1701320	rs8059926	MAPK8IP3	p13.3	0.451	0.286
SNP_A-8656410	16	1705214	rs7197815	MAPK8IP3	p13.3	0.186	0.524
SNP_A-1807499	16	1724143	rs8049415	MAPK8IP3	p13.3	0.202	0.349
SNP_A-8304299	16	1752973	rs2294616	MAPK8IP3	p13.3	0.154	0.892
SNP_A-4254678	16	1757432	rs2575369	MAPK8IP3	p13.3	0.432	0.610
SNP_A-1845900	16	23761929	rs2188360	PRKCB	p12.1	0.248	0.978
SNP_A-8374349	16	23772091	rs7404095	PRKCB	p12.1	0.437	0.844
SNP_A-2070924	16	23772225	rs7404005	PRKCB	p12.1	0.230	0.542
SNP_A-8490323	16	23773033	rs2106375	PRKCB	p12.1	0.208	0.667
SNP_A-4292296	16	23773724	rs8056879	PRKCB	p12.1	0.365	0.663
SNP_A-2089348	16	23773826	rs17809041	PRKCB	p12.1	0.109	0.573
SNP_A-4298603	16	23774158	rs3785404	PRKCB	p12.1	0.158	0.876
SNP_A-1876648	16	23774414	rs11074583	PRKCB	p12.1	0.441	0.557
SNP_A-2176135	16	23774524	rs3785403	PRKCB	p12.1	0.387	0.955
SNP_A-4248739	16	23775277	rs2188355	PRKCB	p12.1	0.386	0.903
SNP_A-1881140	16	23777018	rs10852256	PRKCB	p12.1	0.443	0.252

SNP_A-4257477	16	23784730	rs3826260	PRKCB	p12.1	0.209	0.816
SNP_A-8588489	16	23784990	rs3826259	PRKCB	p12.1	0.492	0.930
SNP_A-4196839	16	23789545	rs8047317	PRKCB	p12.1	0.444	0.735
SNP_A-1785710	16	23790049	rs1468130	PRKCB	p12.1	0.496	0.446
SNP_A-8530187	16	23795684	rs9940072	PRKCB	p12.1	0.499	0.445
SNP_A-8583383	16	23798236	rs4592664	PRKCB	p12.1	0.183	0.197
SNP_A-2181637	16	23799646	rs1557671	PRKCB	p12.1	0.242	0.985
SNP_A-8622917	16	23810657	rs3785396	PRKCB	p12.1	0.267	0.231
SNP_A-8369294	16	23817486	rs11644907	PRKCB	p12.1	0.324	0.293
SNP_A-8414453	16	23819637	rs10775269	PRKCB	p12.1	0.430	0.255
SNP_A-8402079	16	23831007	rs1858871	PRKCB	p12.1	0.419	0.488
SNP_A-2050242	16	23832068	rs6497704	PRKCB	p12.1	0.051	0.245
SNP_A-2004623	16	23833975	rs3785394	PRKCB	p12.1	0.369	0.618
SNP_A-2064728	16	23839214	rs2188356	PRKCB	p12.1	0.447	0.263
SNP_A-1789890	16	23846939	rs12932420	PRKCB	p12.1	0.439	0.196
SNP_A-1860175	16	23852120	rs8051531	PRKCB	p12.1	0.385	0.691
SNP_A-1890150	16	23852213	rs8051700	PRKCB	p12.1	0.431	0.607
SNP_A-1866212	16	23857413	rs8053880	PRKCB	p12.1	0.381	0.700
SNP_A-2248922	16	23857686	rs8055831	PRKCB	p12.1	0.380	0.652
SNP_A-2172009	16	23861629	rs17810486	PRKCB	p12.1	0.058	0.162
SNP_A-1915601	16	23862011	rs195996	PRKCB	p12.1	0.419	0.842
SNP_A-8550101	16	23864466	rs195999	PRKCB	p12.1	0.431	0.478
SNP_A-1827542	16	23866472	rs7196543	PRKCB	p12.1	0.364	0.592
SNP_A-4297289	16	23866921	rs1989647	PRKCB	p12.1	0.363	0.833
SNP_A-2093948	16	23871505	rs9940479	PRKCB	p12.1	0.153	0.630
SNP_A-2140826	16	23871593	rs120908	PRKCB	p12.1	0.398	0.520
SNP_A-2227424	16	23873587	rs196004	PRKCB	p12.1	0.399	0.409
SNP_A-1890610	16	23883794	rs4238948	PRKCB	p12.1	0.364	0.251
SNP_A-1900528	16	23884492	rs196008	PRKCB	p12.1	0.493	0.516
SNP_A-8312987	16	23885388	rs886116	PRKCB	p12.1	0.066	0.406
SNP_A-2112564	16	23891757	rs2340988	PRKCB	p12.1	0.463	0.266
SNP_A-8601754	16	23893896	rs2560401	PRKCB	p12.1	0.050	0.658
SNP_A-1797460	16	23894721	rs2560402	PRKCB	p12.1	0.161	0.081
SNP_A-8432561	16	23896190	rs196012	PRKCB	p12.1	0.205	0.612
SNP_A-8639169	16	23897168	rs196015	PRKCB	p12.1	0.168	0.540
SNP_A-2111531	16	23905489	rs7197785	PRKCB	p12.1	0.431	0.614
SNP_A-1901391	16	23914288	rs4788192	PRKCB	p12.1	0.393	0.939
SNP_A-1900564	16	23921025	rs7192816	PRKCB	p12.1	0.393	0.990
SNP_A-1817659	16	23922112	rs11074598	PRKCB	p12.1	0.435	0.376
SNP_A-8312993	16	23923602	rs10492795	PRKCB	p12.1	0.060	0.202
SNP_A-8600763	16	23925135	rs195992	PRKCB	p12.1	0.082	0.037
SNP_A-1821397	16	23926364	rs4788423	PRKCB	p12.1	0.358	0.897
SNP_A-2273154	16	23926713	rs8055243	PRKCB	p12.1	0.330	0.919
SNP_A-8533554	16	23930898	rs17811655	PRKCB	p12.1	0.135	0.436
SNP_A-4268738	16	23931809	rs4788426	PRKCB	p12.1	0.342	0.520
SNP_A-8532776	16	23937663	rs11865731	PRKCB	p12.1	0.250	0.159
SNP_A-8298736	16	23941146	rs7199551	PRKCB	p12.1	0.413	0.792
SNP_A-8427783	16	23942936	rs7188812	PRKCB	p12.1	0.297	0.168
SNP_A-8593480	16	23946409	rs12445528	PRKCB	p12.1	0.064	0.305
SNP_A-8717447	16	23946514	rs7202459	PRKCB	p12.1	0.280	0.356
SNP_A-1782983	16	23953095	rs4787291	PRKCB	p12.1	0.193	0.956
SNP_A-8676193	16	23957189	rs2046892	PRKCB	p12.1	0.461	0.117
SNP_A-2185697	16	23965640	rs16940401	PRKCB	p12.1	0.152	0.321
SNP_A-8416794	16	23967796	rs17812348	PRKCB	p12.1	0.213	0.242
SNP_A-4242819	16	23978645	rs8051750	PRKCB	p12.1	0.158	0.648
SNP_A-8290202	16	23978982	rs7193148	PRKCB	p12.1	0.158	0.681
SNP_A-2079303	16	23994362	rs9923820	PRKCB	p12.1	0.055	0.918
SNP_A-4193350	16	23995885	rs9938298	PRKCB	p12.1	0.246	0.228
SNP_A-8353462	16	24006028	rs6497721	PRKCB	p12.1	0.084	0.088
SNP_A-2238056	16	24007245	rs1014632	PRKCB	p12.1	0.438	0.695
SNP_A-2029202	16	24010063	rs2560406	PRKCB	p12.1	0.440	0.571
SNP_A-8571686	16	24011478	rs9928102	PRKCB	p12.1	0.076	0.805
SNP_A-2044622	16	24022987	rs405322	PRKCB	p12.1	0.480	0.903
SNP_A-8425689	16	24023323	rs392715	PRKCB	p12.1	0.338	0.329
SNP_A-4243810	16	24024978	rs2470688	PRKCB	p12.1	0.480	0.967
SNP_A-1848989	16	24035866	rs174828	PRKCB	p12.1	0.482	0.993
SNP_A-8524392	16	24035888	rs198197	PRKCB	p12.1	0.419	0.972
SNP_A-8491715	16	24036955	rs198199	PRKCB	p12.1	0.236	0.219
SNP_A-8630995	16	24037686	rs9937112	PRKCB	p12.1	0.088	0.364
SNP_A-2030963	16	24039886	rs198182	PRKCB	p12.1	0.237	0.224
SNP_A-8303509	16	24040070	rs11074606	PRKCB	p12.1	0.303	0.554
SNP_A-8613070	16	24041822	rs9939028	PRKCB	p12.1	0.312	0.733
SNP_A-4293880	16	24042613	rs1013316	PRKCB	p12.1	0.358	0.632
SNP_A-8629437	16	24043702	rs198188	PRKCB	p12.1	0.482	0.158

SNP_A-4242825	16	24052529	rs375624	PRKCB	p12.1	0.341	0.353
SNP_A-1921094	16	24056542	rs198202	PRKCB	p12.1	0.348	0.271
SNP_A-1863454	16	24056638	rs16973277	PRKCB	p12.1	0.091	0.310
SNP_A-1797251	16	24059968	rs381901	PRKCB	p12.1	0.260	0.345
SNP_A-2030375	16	24064447	rs2238493	PRKCB	p12.1	0.099	0.618
SNP_A-2024152	16	24064671	rs400066	PRKCB	p12.1	0.355	0.751
SNP_A-8466968	16	24065071	rs416951	PRKCB	p12.1	0.352	0.752
SNP_A-4194607	16	24066835	rs430151	PRKCB	p12.1	0.354	0.775
SNP_A-4234949	16	24071789	rs408882	PRKCB	p12.1	0.356	0.728
SNP_A-2078655	16	24072225	rs373634	PRKCB	p12.1	0.244	0.768
SNP_A-1944736	16	24072424	rs377133	PRKCB	p12.1	0.355	0.838
SNP_A-8701863	16	24086743	rs2283548	PRKCB	p12.1	0.246	0.270
SNP_A-8475113	16	24094062	rs11649514	PRKCB	p12.1	0.126	0.159
SNP_A-8290204	16	24104683	rs2239344	PRKCB	p12.1	0.355	0.704
SNP_A-1886429	16	24106351	rs198142	PRKCB	p12.1	0.059	0.539
SNP_A-8672640	16	24109959	rs3729904	PRKCB	p12.1	0.268	0.261
SNP_A-8702073	16	24110116	rs198145	PRKCB	p12.1	0.415	0.477
SNP_A-8552188	16	24115010	rs1548384	PRKCB	p12.1	0.190	0.978
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SNP_A-2269698	16	24118877	rs437545	PRKCB	p12.1	0.082	0.949
SNP_A-8536185	16	24121088	rs12445719	PRKCB	p12.1	0.128	0.976
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SNP_A-1857696	16	24129259	rs10852263	PRKCB	p12.1	0.210	0.370
SNP_A-1871220	16	24134241	rs3785380	PRKCB	p12.1	0.056	0.953
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SNP_A-8474677	17	3710682	rs9135	CAMKK1	p13.2	0.485	0.922
SNP_A-8313730	17	3728542	rs8065798	CAMKK1	p13.2	0.461	0.083
SNP_A-8302477	17	3733656	rs758642	CAMKK1	p13.2	0.348	0.690
SNP_A-8709961	17	3740196	rs753512	CAMKK1	p13.2	0.305	0.307
SNP_A-8605871	17	11871706	rs8067785	MAP2K4	p12	0.131	0.832
SNP_A-1839176	17	11875751	rs17613899	MAP2K4	p12	0.070	0.514
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SNP_A-2146686	17	11925064	rs9907196	MAP2K4	p12	0.229	0.448
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SNP_A-8287493	17	11965072	rs2108496	MAP2K4	p12	0.282	0.989
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SNP_A-1896113	17	21143931	rs12451239	MAP2K3	p11.2	0.200	0.243
SNP_A-1866779	17	21154375	rs9901404	MAP2K3	p11.2	0.493	0.054
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SNP_A-8635525	17	21157832	rs4114291	MAP2K3	p11.2	0.451	0.333
SNP_A-2245106	17	40702763	rs4792809	MAP3K14	q21.31	0.265	0.235
SNP_A-8563382	17	40703393	rs11574831	MAP3K14	q21.31	0.140	0.527
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SNP_A-8654263	17	40744196	rs17686001	MAP3K14	q21.31	0.175	0.559
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SNP_A-1921805	17	61733114	rs12601850	PRKCA	q24.2	0.417	0.586
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SNP_A-8395590	17	61763024	rs7218425	PRKCA	q24.2	0.267	0.689

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SNP_A-2099497	17	61813793	rs4536508	PRKCA	q24.2	0.139	0.305
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SNP_A-1955964	17	61839105	rs4630585	PRKCA	q24.2	0.111	0.527
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SNP_A-8646906	17	61841876	rs16959227	PRKCA	q24.2	0.099	0.992
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SNP_A-1959432	17	61844384	rs16959229	PRKCA	q24.2	0.143	0.825
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SNP_A-4244095	17	61850787	rs7502206	PRKCA	q24.2	0.081	0.270
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SNP_A-4287828	17	61861309	rs6504432	PRKCA	q24.2	0.079	0.311
SNP_A-2291229	17	61862056	rs7405806	PRKCA	q24.2	0.352	0.906
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SNP_A-2121258	17	61870469	rs990082	PRKCA	q24.2	0.283	0.370
SNP_A-2053164	17	61870528	rs990083	PRKCA	q24.2	0.308	0.420
SNP_A-2256224	17	61874091	rs228884	PRKCA	q24.2	0.416	0.605
SNP_A-8447977	17	61878183	rs12452749	PRKCA	q24.2	0.053	0.568
SNP_A-8629006	17	61878733	rs4082895	PRKCA	q24.2	0.420	0.035
SNP_A-2241731	17	61883690	rs17771145	PRKCA	q24.2	0.129	0.509
SNP_A-8382030	17	61885383	rs11869711	PRKCA	q24.2	0.093	0.211
SNP_A-2060532	17	61885422	rs7221805	PRKCA	q24.2	0.398	0.035
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SNP_A-2127143	17	61907910	rs34488708	PRKCA	q24.2	0.195	0.155
SNP_A-4201798	17	61911986	rs3848418	PRKCA	q24.2	0.390	0.102
SNP_A-1783252	17	61912594	rs7224628	PRKCA	q24.2	0.371	0.093
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SNP_A-4292811	17	61942803	rs16959447	PRKCA	q24.2	0.181	0.842
SNP_A-2180370	17	61944200	rs16959450	PRKCA	q24.2	0.181	0.849
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SNP_A-1873918	17	61948969	rs956952	PRKCA	q24.2	0.187	0.894
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SNP_A-2294345	17	61949893	rs16959510	PRKCA	q24.2	0.191	0.890
SNP_A-2097923	17	61952114	rs16959514	PRKCA	q24.2	0.184	0.981
SNP_A-8303780	17	61956857	rs1806448	PRKCA	q24.2	0.243	0.457
SNP_A-2087723	17	61960104	rs6504441	PRKCA	q24.2	0.330	0.628
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SNP_A-4193637	17	61963519	rs9908167	PRKCA	q24.2	0.391	0.192
SNP_A-8404731	17	61965362	rs9303510	PRKCA	q24.2	0.228	0.469
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SNP_A-4216996	17	61968793	rs4791051	PRKCA	q24.2	0.470	0.400
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SNP_A-8460686	17	61976025	rs1533344	PRKCA	q24.2	0.084	0.222
SNP_A-8597495	17	61976115	rs11658528	PRKCA	q24.2	0.080	0.663

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SNP_A-2200892	17	61977504	rs16959604	PRKCA	q24.2	0.131	0.887
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SNP_A-8441385	17	61984879	rs16959643	PRKCA	q24.2	0.259	0.841
SNP_A-1914091	17	61997624	rs7219499	PRKCA	q24.2	0.491	0.753
SNP_A-2118344	17	61999089	rs8066055	PRKCA	q24.2	0.491	0.664
SNP_A-1811249	17	62002932	rs9904266	PRKCA	q24.2	0.489	0.895
SNP_A-8499176	17	62003178	rs9905351	PRKCA	q24.2	0.419	0.685
SNP_A-2152891	17	62005044	rs8069859	PRKCA	q24.2	0.163	0.458
SNP_A-1928161	17	62005954	rs9900353	PRKCA	q24.2	0.498	0.936
SNP_A-8695792	17	62007136	rs16969771	PRKCA	q24.2	0.162	0.345
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SNP_A-4283037	17	62009399	rs41493450	PRKCA	q24.2	0.114	0.241
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SNP_A-8654964	17	62030661	rs17759410	PRKCA	q24.2	0.159	0.283
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SNP_A-8384953	17	62037186	rs9908814	PRKCA	q24.2	0.193	0.115
SNP_A-4243757	17	62037797	rs227915	PRKCA	q24.2	0.159	0.922
SNP_A-8403981	17	62037856	rs227913	PRKCA	q24.2	0.353	0.227
SNP_A-8403980	17	62038189	rs170586	PRKCA	q24.2	0.441	0.664
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SNP_A-8439372	17	62114727	rs17689224	PRKCA	q24.2	0.204	0.436
SNP_A-8440229	17	62115027	rs1010546	PRKCA	q24.2	0.117	0.175
SNP_A-4251177	17	62117908	rs1010544	PRKCA	q24.2	0.245	0.203
SNP_A-8331770	17	62128843	rs9912033	PRKCA	q24.2	0.170	0.772
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SNP_A-4251175	17	62133841	rs7217618	PRKCA	q24.2	0.456	0.387
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SNP_A-8474698	17	62164112	rs16960132	PRKCA	q24.2	0.095	0.036
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SNP_A-1942977	17	62201284	rs17643302	PRKCA	q24.2	0.084	0.169
SNP_A-8427742	17	62203761	rs4528612	PRKCA	q24.2	0.226	0.220
SNP_A-1867018	17	62204090	rs17710992	PRKCA	q24.2	0.308	0.510
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SNP_A-2084000	17	62214665	rs9890888	PRKCA	q24.2	0.085	0.425
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SNP_A-2131637	17	64021487	rs4265886	PRKAR1A	q24.2	0.356	0.581
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SNP_A-8470906	17	64023836	rs4281788	PRKAR1A	q24.2	0.210	0.651
SNP_A-2080107	17	64024620	rs8076465	PRKAR1A	q24.2	0.356	0.319
SNP_A-1850614	17	64030258	rs2952275	PRKAR1A	q24.2	0.359	0.516
SNP_A-4229112	17	64035235	rs3785906	PRKAR1A	q24.2	0.208	0.606
SNP_A-2106125	17	64041374	rs2952271	FAM20A	q24.2	0.357	0.330
SNP_A-1873320	17	64042744	rs2952270	FAM20A	q24.2	0.300	0.385
SNP_A-2146656	17	64049834	rs2302234	FAM20A	q24.2	0.293	0.511
SNP_A-1936451	17	64050013	rs2302235	FAM20A	q24.2	0.141	0.765
SNP_A-1868880	17	64051030	rs10491176	FAM20A	q24.2	0.131	0.407
SNP_A-1868881	17	64051442	rs2286562	FAM20A	q24.2	0.166	0.148
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SNP_A-2313584	17	64924711	rs817547	MAP2K6	q24.3	0.428	0.571
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SNP_A-8303630	17	64954463	rs6501326	MAP2K6	q24.3	0.494	0.049
SNP_A-8541255	17	64976884	rs2521367	MAP2K6	q24.3	0.343	0.865
SNP_A-2280275	17	64979552	rs2716225	MAP2K6	q24.3	0.489	0.894
SNP_A-8495526	17	64981043	rs12945375	MAP2K6	q24.3	0.173	0.326
SNP_A-8422667	17	64981435	rs2715814	MAP2K6	q24.3	0.485	0.822
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SNP_A-8547723	17	65001825	rs739559	MAP2K6	q24.3	0.405	0.632
SNP_A-2240714	17	65013733	rs2074027	MAP2K6	q24.3	0.425	0.202
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SNP_A-2211448	17	65033094	rs17691066	MAP2K6	q24.3	0.065	0.669
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SNP_A-2092702	17	65037811	rs11869376	MAP2K6	q24.3	0.194	0.143
SNP_A-8657651	17	65038344	rs2716197	MAP2K6	q24.3	0.417	0.625
SNP_A-8611015	17	65047718	rs12600726	MAP2K6	q24.3	0.169	0.655
SNP_A-2042052	18	46346987	rs4939634	MAPK4	q21.1	0.479	0.869
SNP_A-4271010	18	46347255	rs4939635	MAPK4	q21.1	0.479	0.775
SNP_A-1910699	18	46350750	rs8089517	MAPK4	q21.1	0.474	0.788
SNP_A-1910701	18	46351008	rs8093289	MAPK4	q21.1	0.193	0.798
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SNP_A-2029495	18	46358644	rs4081996	MAPK4	q21.1	0.441	0.672
SNP_A-2077720	18	46358871	rs6508009	MAPK4	q21.1	0.441	0.672
SNP_A-8443809	18	46360410	rs2338830	MAPK4	q21.1	0.245	0.516
SNP_A-1840856	18	46363323	rs4939637	MAPK4	q21.1	0.276	0.174
SNP_A-2084294	18	46365043	rs10432161	MAPK4	q21.1	0.246	0.068
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SNP_A-4227612	18	46365939	rs1370480	MAPK4	q21.1	0.246	0.068
SNP_A-1843099	18	46372358	rs4322755	MAPK4	q21.1	0.471	0.805
SNP_A-2146390	18	46377759	rs930362	MAPK4	q21.1	0.287	0.339
SNP_A-2307651	18	46378713	rs992595	MAPK4	q21.1	0.473	0.785
SNP_A-1947210	18	46378761	rs17742008	MAPK4	q21.1	0.212	0.484
SNP_A-8310896	18	46383685	rs1437650	MAPK4	q21.1	0.483	0.581
SNP_A-4256042	18	46384530	rs10502909	MAPK4	q21.1	0.318	0.923
SNP_A-4259820	18	46384859	rs3862671	MAPK4	q21.1	0.483	0.756
SNP_A-1948352	18	46394236	rs4599004	MAPK4	q21.1	0.220	0.446
SNP_A-8540435	18	46398569	rs17742138	MAPK4	q21.1	0.244	0.637
SNP_A-2063695	18	46401874	rs1025688	MAPK4	q21.2	0.410	0.592
SNP_A-4250076	18	46402020	rs1437648	MAPK4	q21.2	0.347	0.191
SNP_A-1865911	18	46406082	rs4939992	MAPK4	q21.2	0.067	0.440
SNP_A-1903084	18	46409165	rs9304402	MAPK4	q21.2	0.483	0.694
SNP_A-1800249	18	46411251	rs12604601	MAPK4	q21.2	0.294	0.672
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SNP_A-1961567	18	46413307	rs4939996	MAPK4	q21.2	0.359	0.247
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SNP_A-8382084	18	46416077	rs12454262	MAPK4	q21.2	0.316	0.928
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SNP_A-4283499	18	46419749	rs17804574	MAPK4	q21.2	0.299	0.988
SNP_A-1913499	18	46420290	rs973644	MAPK4	q21.2	0.170	0.853
SNP_A-4250717	18	46420554	rs893316	MAPK4	q21.2	0.218	0.507
SNP_A-2220756	18	46420686	rs934746	MAPK4	q21.2	0.095	0.491
SNP_A-8536496	18	46429046	rs12958523	MAPK4	q21.2	0.429	0.828
SNP_A-8519820	18	46431858	rs11662176	MAPK4	q21.2	0.328	0.938
SNP_A-8330623	18	46434954	rs7235791	MAPK4	q21.2	0.254	0.987
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SNP_A-8333032	18	46445557	rs8097986	MAPK4	q21.2	0.473	0.424
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SNP_A-1915587	18	46474454	rs17742551	MAPK4	q21.2	0.109	0.275
SNP_A-2276340	18	46474527	rs1545130	MAPK4	q21.2	0.496	0.519
SNP_A-8712770	18	46476105	rs17804724	MAPK4	q21.2	0.108	0.240
SNP_A-8527554	18	46494835	rs12959952	MAPK4	q21.2	0.407	0.368
SNP_A-8648704	18	46497759	rs3794897	MAPK4	q21.2	0.326	0.867
SNP_A-8287196	19	43780301	rs7251456	MAP4K1	q13.2	0.117	0.548
SNP_A-1784555	19	45393021	rs10402740	MAP3K10	q13.2	0.233	0.431
SNP_A-8655530	19	45403173	rs892117	MAP3K10	q13.2	0.500	1.000
SNP_A-8596766	19	59083494	rs307952	PRKCG	q13.41	0.281	0.409
SNP_A-8556976	19	59089466	rs8103851	PRKCG	q13.41	0.396	0.843
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SNP_A-8524335	20	42597752	rs3092590	PKIG	q13.12	0.095	0.108
SNP_A-8465870	20	42612081	rs11086929	PKIG	q13.12	0.055	0.384
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SNP_A-8323666	20	42641966	rs1547430	PKIG	q13.12	0.442	0.401
SNP_A-8651892	20	42643249	rs2027871	PKIG	q13.12	0.435	0.665
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SNP_A-4260238	20	42660410	rs244097	PKIG	q13.12	0.151	0.556
SNP_A-8604494	20	42662198	rs244096	PKIG	q13.12	0.147	0.904
SNP_A-8518959	22	20445004	rs6928	MAPK1	q11.21	0.439	0.686
SNP_A-8651504	22	20451327	rs5755074	MAPK1	q11.21	0.052	0.271
SNP_A-8587058	22	20451554	rs2266966	MAPK1	q11.21	0.440	0.709
SNP_A-4244267	22	20452149	rs17759598	MAPK1	q11.21	0.166	0.535
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SNP_A-8614321	22	20481821	rs9610338	MAPK1	q11.21	0.438	0.556
SNP_A-4298195	22	20483239	rs2298434	MAPK1	q11.21	0.053	0.064

SNP_A-4201707	22	20487661	rs5749986	MAPK1	q11.21	0.438	0.584
SNP_A-8579523	22	20510183	rs7286558	MAPK1	q11.22	0.071	0.256
SNP_A-4253585	22	20517660	rs5999749	MAPK1	q11.22	0.437	0.483
SNP_A-2046461	22	20520163	rs17759796	MAPK1	q11.22	0.166	0.363
SNP_A-1876854	22	20530530	rs5755694	MAPK1	q11.22	0.415	0.157
SNP_A-8497959	22	20539139	rs9610470	MAPK1	q11.22	0.237	0.138
SNP_A-8428219	22	20543969	rs9610487	MAPK1	q11.22	0.237	0.135
SNP_A-8693764	22	36793087	rs3026688	PICK1	q13.1	0.258	0.556

Supporting Information

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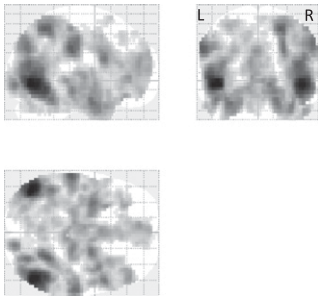

Fig. S1. Genotype-independent, subsequent memory analysis for negative information, thresholded at $P < 0.05$, FDR corrected for whole brain. Sagittal, coronal, and axial SPM glass-brain projections are shown. L, left side of the brain; R, right side of the brain.

Table S1. Nominal significance of associated SNPs (negative pictures free recall, $P_{uncorrected} < 0.01$) in the hypothesis-testing sample ($n = 723$)

Affymetrix marker	Chromosome	Position	dbSNP RS ID	Associated gene	Cytoband	Call rate	MAF	HWE *P*	Association *P*
SNP_A-8703022	**17**	**62,209,616**	**rs4790904**	***PRKCA***	**q24.2**	**0.997**	**0.20**	**0.697077012**	**0.000002**
SNP_A-1995659	10	12,875,051	rs928337	*CAMK1D*	p13	1.000	0.41	0.353067038	0.00078
SNP_A-1995661	10	12,875,594	rs2493766	*CAMK1D*	p13	0.999	0.37	0.716531688	0.00081
SNP_A-1806035	10	12,887,844	rs4750267	*CAMK1D*	p13	0.997	0.37	0.80609225	0.0012
SNP_A-1936417	10	12,880,848	rs1556408	*CAMK1D*	p13	0.997	0.37	0.797212222	0.0013
SNP_A-8659980	10	12,891,662	rs12358381	*CAMK1D*	p13	1.000	0.27	0.049411446	0.0014
SNP_A-1985684	6	36,127,314	rs17714205	*MAPK14*	p21.31	0.997	0.13	0.524852836	0.0017
SNP_A-8281277	10	12,874,932	rs928336	*CAMK1D*	p13	0.994	0.43	0.170919012	0.0019
SNP_A-2111454	10	12,890,474	rs10906229	*CAMK1D*	p13	0.999	0.35	0.714469219	0.0020
SNP_A-2108498	6	36,184,912	rs3804452	*MAPK14*	p21.31	0.999	0.13	0.550959233	0.0024
SNP_A-2222070	17	62,147,088	rs16960114	*PRKCA*	q24.2	0.993	0.20	0.780677016	0.0028
SNP_A-8281665	10	12,876,558	rs1929389	*CAMK1D*	p13	1.000	0.43	0.18044124	0.0030
SNP_A-1816092	10	49,265,870	rs17697960	*MAPK8*	q11.22	1.000	0.11	0.148347676	0.0033
SNP_A-2000443	10	49,312,216	rs7086275	*MAPK8*	q11.22	0.999	0.42	0.628650983	0.0041
SNP_A-4248684	10	49,290,273	rs9888128	*MAPK8*	q11.22	1.000	0.43	0.729951509	0.0045
SNP_A-2000441	10	49,312,152	rs11101320	*MAPK8*	q11.22	0.994	0.42	0.661763446	0.0047
SNP_A-1781918	10	49,264,246	rs10857560	*MAPK8*	q11.22	0.999	0.43	0.395575993	0.0048
SNP_A-8637914	17	61,737,476	rs7210446	*PRKCA*	q24.2	0.990	0.44	0.87454757	0.0049
SNP_A-4229112	17	64,035,235	rs3785906	*PRKAR1A*	q24.2	1.000	0.23	0.815795241	0.0054
SNP_A-8550960	7	151,186,459	rs6961830	*PRKAG2*	q36.1	0.994	0.18	0.93078015	0.0056
SNP_A-1931100	10	12,872,599	rs4747999	*CAMK1D*	p13	1.000	0.41	0.250623163	0.0056
SNP_A-8470906	17	64,023,836	rs4281788	*PRKAR1A*	q24.2	0.999	0.23	0.770857219	0.0061
SNP_A-2163878	10	49,261,724	rs2698761	*MAPK8*	q11.22	1.000	0.43	0.747074632	0.0062
SNP_A-4222841	10	49,220,700	rs6537561	*MAPK8*	q11.22	1.000	0.43	0.864461361	0.0064
SNP_A-8676867	6	161,418,462	rs9458114	*MAP3K4*	q26	0.997	0.07	0.45633922	0.0077
SNP_A-4292124	10	6,539,234	rs4750491	*PRKCQ*	p15.1	0.994	0.34	0.052291675	0.0081
SNP_A-2146600	17	62,196,905	rs4381631	*PRKCA*	q24.2	0.999	0.47	0.596302414	0.0082
SNP_A-2055994	17	62,148,632	rs4465636	*PRKCA*	q24.2	0.994	0.20	0.584940644	0.0093
SNP_A-2237869	10	12,686,538	rs7906212	*CAMK1D*	p13	0.990	0.07	0.752773631	0.0095
SNP_A-8330608	17	61,738,935	rs4577128	*PRKCA*	q24.2	1.000	0.44	0.583248971	0.0096
SNP_A-8366935	6	161,338,632	rs625977	*MAP3K4*	q26	1.000	0.17	0.586805235	0.0099

Bonferroni-corrected SNPs are in boldface type. HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; dbSNP RS, reference SNP sequence number according the National Center for Biotechnology Information SNP data base.

Table S2. Genotype-dependent differences in arousal and valence ratings (n = 716)

Genotype, rs4790904	Arousal negative pictures, mean ± SEM	Valence negative pictures, mean ± SEM
AA, n = 456	1.67 ± 0.02	2.78 ± 0.01
AG, n = 229	1.67 ± 0.02	2.79 ± 0.01
GG, n = 31	1.64 ± 0.07	2.76 ± 0.04
	P = 0.9	P = 0.8

Table S3. Genotype-dependent performance in the 0- and 2-back task (n = 678)

Genotype, rs4790904	Accuracy, 0-back, mean ± SEM	Accuracy, 2-back, mean ± SEM
AA, n = 428	0.964 ± 0.002	0.869 ± 0.005
AG, n = 219	0.962 ± 0.002	0.873 ± 0.006
GG, n = 31	0.971 ± 0.04	0.874 ± 0.016
	P = 0.9	P = 0.6

Table S4. Genotype-dependent memory performance (24-h delay) in the hypothesis-testing sample (n = 719)

Genotype, rs4790904	Negative pictures, mean ± SEM	Positive pictures, mean ± SEM	Neutral pictures, mean ± SEM	All pictures, mean ± SEM
AA, n = 456	7.7 ± 0.2	8.1 ± 0.2	4.8 ± 0.1	20.7 ± 0.4
AG, n = 231	7.0 ± 0.2	7.8 ± 0.2	4.2 ± 0.2	19.0 ± 0.5
GG, n = 32	5.6 ± 0.4	7.1 ± 0.4	3.7 ± 0.5	16.4 ± 0.8
	P = 0.0001	P = 0.07	P = 0.0006	P = 0.0004

4.5. THE ASSOCIATION OF THE BDNF VAL66MET POLYMORPHISM AND THE HIPPOCAMPAL VOLUMES IN HEALTHY HUMANS: A JOINT META-ANALYSIS OF PUBLISHED AND NEW DATA

Harrisberger, F. [*], Spalek, K.[*], Smieskova, R., Schmid, A., Coynel, D., Milnik, A., Fastenrath, M., Freytag, V., Gschwind, L., Walter, A., Vogel, T., Bendfeldt, K., de Quervain, D.J.-F., Papassotiropoulos, A., & Borgwardt, S. (2014). *Neuroscience and Biobehavioral Reviews*, *42C*, 267-278.

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Review

The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data

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ABSTRACT

Background: The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (refSNP Cluster Report: rs6265) is a common and functionally relevant single nucleotide polymorphism (SNP). The gene itself, as well as the SNP rs6265, have been implicated in hippocampal learning and memory. However, imaging genetic studies have produced controversial results about the impact of this SNP on hippocampal volumes in healthy subjects.
Methods: We examined the association between the rs6265 polymorphism and hippocampal volume in 643 healthy young subjects using automatic segmentation and subsequently included these data in a meta-analysis based on published studies with 5298 healthy subjects in total.
Results: We found no significant association between SNP rs6265 and hippocampal volumes in our sample ($g = 0.05$, $p = 0.58$). The meta-analysis revealed a small, albeit significant difference in hippocampal volumes between genotype groups, such that Met-carriers had slightly smaller hippocampal volumes than Val/Val homozygotes ($g = 0.09$, $p = 0.04$), an association that was only evident when manual ($g = 0.22$, $p = 0.01$) but not automatic tracing approaches ($g = 0.04$, $p = 0.38$) were used. Studies using manual tracing showed evidence for publication bias and a significant decrease in effect size over the years with increasing sample sizes.
Conclusions: This study does not support the association between SNP rs6265 and hippocampal volume in healthy individuals. The weakly significant effect observed in the meta-analysis is mainly driven by studies with small sample sizes. In contrast, our original data and the meta-analysis of automatically segmented hippocampal volumes, which was based on studies with large samples sizes, revealed no significant genotype effect. Thus, meta-analyses of the association between rs6265 and hippocampal volumes should consider possible biases related to measuring technique and sample size.

Contents

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1. Introduction

Brain-derived neurotrophic factor (BDNF) – a member of the nerve growth factor family – plays an important role in neurogenesis and is implicated in several molecular processes in the central nervous system (Barde et al., 1982; Lu and Gottschalk, 2000; Park and Poo, 2013). BDNF is highly expressed in the hippocampus, a key region for adult neurogenesis (De Quervain and Papassotiropoulos, 2006; Milner et al., 1998), and is thought to be involved in learning and memory (Cunha et al., 2010). Pro-BDNF can induce apoptosis, while mature BDNF predominantly mediates cell survival and neuronal differentiation (Pang et al., 2004; Korte et al., 1995; Pastalkova et al., 2006). The single nucleotide polymorphism (SNP) rs6265 at codon 66 of the *BDNF* gene predicts a valine (Val) to methionine (Met) substitution in the pro-region of the protein, which is important for proper BDNF sorting. The Val66Met substitution has been investigated in a transgenic mouse model of defective BDNF secretion in hippocampal neurons (Chen et al., 2004; Egan et al., 2003). BDNF Met/Met mice have smaller hippocampal volumes, less dendritic arbor complexity of hippocampal neurons and impaired synaptic plasticity, as indicated by a decrease in NMDA-receptor-dependent long-term depression and long-term potentiation (Chen et al., 2006; Ninan et al., 2010).

Defects in synaptic plasticity and long-term potentiation, core mechanisms of hippocampus-dependent learning and memory, are thought to underlie – at least in part – neurocognitive impairments in a broad spectrum of neuropsychiatric disorders (Fusar-Poli et al., 2012; Lu et al., 2013). Another characteristic of neuropsychiatric disorders, such as schizophrenia, bipolar disorder, depression, post-traumatic stress disorders and personality disorders, is the reduction in hippocampal volume (Geuze et al., 2005; Smieskova et al., 2010; Walter et al., 2012). It is still not clear to what extent these hippocampal volume abnormalities are driven by genetic liability (Sullivan et al., 2003). One putative genetic risk factor of these alterations might be the BDNF polymorphism described above (Boulle et al., 2012; Frielingsdorf et al., 2010). The effect of this polymorphism has often been studied in healthy subjects, because in a healthy population, changes in brain volumes are independent of effects of illness or medication, and of disease-related genetic risk factors (Fusar-Poli et al., 2013; Smieskova et al., 2009).

To date findings from structural magnetic resonance imaging (sMRI) studies investigating genotype-dependent association of rs6265 SNP on hippocampal volumes are inconsistent. While three recent meta-analyses report that Met-carriers have smaller hippocampal volumes than Val/Val homozygotes (Hajek et al., 2012; Kambeitz et al., 2012; Molendijk et al., 2012a), the relation between rs6265 and hippocampal volumes is confounded by several problems: Firstly, two of these studies (Kambeitz et al., 2012; Molendijk et al., 2012a) included a variety of neurocognitive disorders, suggesting that hippocampal volumes were probably affected by burden of illness, medication or comorbid conditions and were not necessarily related to the SNP per se. Secondly, all of these meta-analyses incorporated studies with children/adolescents and elderly subjects. This can be critical, as hippocampal volumes undergo age-related changes (Karnik et al., 2010; Walhovd et al., 2011; Goodro et al., 2012). Finally, although one of the previous meta-analyses focuses exclusively on healthy subjects (Hajek et al., 2012), the analysis in this study was restricted to manual tracing of hippocampal volumes without considering automatic measurement techniques.

The present study aimed to control for these confounding factors. First, we assessed the association between the BDNF rs6265 polymorphism and hippocampal volumes using the automated tracing technique in 643 healthy young volunteers. Because the effect size of this association is known to be small (Kambeitz et al., 2012; Molendijk et al., 2012a), we then increased statistical power by means of meta-analytic techniques (Kim-Cohen et al., 2006; Munafò et al., 2009; Brandys et al., 2011). We therefore performed a systematic review of the hippocampal volumes in healthy subjects genotyped for SNP rs6265 and combined these data with our original results in a meta-analysis. Additionally, we examined the effect of potential moderators such as measuring technique, MR magnetic field strength, age, gender, ethnicity, Val/Met ratio, sample size, quality rating, hippocampal volumes normalized to intracranial volume (ICV), and publication year.

2. Material and methods

2.1. Original data of 643 healthy subjects

2.1.1. Participants

We recruited 643 healthy young subjects (383 women; age range 18–35 years, mean age ± standard deviation (SD) 22.87 ± 3.22). Participants filled in a self-rating questionnaire concerning their health status, medication, and drug consumption. All included subjects were free of any physical, neurological or psychiatric illness, and were taking no medication. 87% of the subjects were students and 91% were right-handed (see Table 1). The ethics committee of the Canton of Basel approved the experiments.

Table 1
Overview of included subjects.

	Val/Val	*N* Val/Val	Val/Met and Met/Met	*N* Val/Met and Met/Met	Statistics	*p*-Value	Effect size*
Age [mean ± SD]	22.75 ± 3.22	413	23.10 ± 3.23	230	$F = 1.72$ df = 1	0.19	0.003
Sex							
Women		254		129	$x^2 = 1.80$	0.18	0.053
Men		159		101	df = 1		
Profession							
In education		361		198	$x^2 = 0.69$	0.71	0.033
Working		35		24	df = 2		
Not in education and without job		12		6			
Handedness							
Right		376		210	$x^2 = 0.01$	0.91	0.004
Left		37		20	df = 1		

* Partial eta (η^2) is reported for age differences, whereas Cramers V is indicated for sex, profession and handedness differences.

Written informed consent was obtained from all subjects prior to participation.

2.1.2. Genotyping

DNA was extracted from saliva samples collected with the Oragene DNA sample collection kit using standard procedures (DNA Genotek Inc., Ontario, Canada). DNA samples were processed on the Affymetrix® Genome-Wide Human SNP Array 6.0. in one centralized microarray facility. rs6265 (refSNP Cluster Report: rs6265) is represented on the array (AFFY|SNP_A-2038925). Generation of SNP calls and array quality control were performed using the Affymetrix Genotyping Console Software 3.0 (Affymetrix Inc.). According to the manufacturer's recommendation, contrast quality control (QC) was chosen as QC metric, using the default value of 0.4. All samples passing QC criteria were subsequently genotyped using the Birdseed (v2) algorithm. Genotypic outliers were identified using Bayesian clustering algorithm (Bellenguez et al., 2012) and excluded (for more details see supplementary material).

2.1.3. Image acquisition and extraction of hippocampal volumes

We acquired an anatomical sequence with a radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence. For this sequence, we used the following acquisition parameters: TE (echo time) = 3.37 ms, FOV (field of view) = 25.6 cm, acquisition matrix = 256 × 256 × 176, voxel size: 1 mm × 1 mm × 1 mm. Using a midsaggital scout image, 176 contiguous axial slices were placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a TR = 2000 ms ($\theta = 8$ degrees).

Segmentations of cortical and subcortical structures were retrieved from FreeSurfer 4.5 and labeling was based on the Desikan–Killiany Atlas (Desikan et al., 2006). We extracted raw volumes for both hippocampi for $n = 805$ subjects. Left and right hippocampal volumes were corrected separately for ICV, age, sex and differences due to software and gradient updates by using the *z*-transformed residuals of a linear regression. Afterwards we did a separate outlier-control for both hippocampal sides (mean ± 3.5 SD). For all subjects with complete dataset, we then calculated the corrected mean value of both hippocampal volumes. For a subgroup of $n = 643$ subjects we had additional genetic information regarding BDNF genotype. The corrected volumetric data of these subjects were included in all further analyses.

2.1.4. Association analysis

For the genetic association analysis, we used the WG-Permer software (www.wg-permer.org), with analysis of variance for quantitative phenotypes. This software corrects nominal *p*-values for multiple testing on a permutation-based procedure according to Westfall and Young (Westfall, 1993).

One-way analyses of variance (ANOVA) and chi-square tests were used to test for differences between genotype groups of age, sex, profession and handedness. These statistical analyses were performed with SPSS (IBM SPSS Statistics, Version 20, 2011). Values are presented as mean ± SD (see Table 1).

2.2. Meta-analysis

2.2.1. Literature search and inclusion criteria

Electronic searches were conducted using PubMed and Embase, considering all publications until the end of December 2012 with the following search terms: "BDNF Val66Met" AND "MRI" and "rs6265" AND "MRI". Additionally, a retrospective search was carried out on the reference lists of the included articles. This resulted in 86 publications, for which the abstracts were screened (more information is presented in Fig. 1). In this meta-analysis, we included healthy groups only. Firstly, we extracted studies addressing the relation between hippocampal volumes and the SNP. Secondly, the papers were filtered according to the following criteria: (a) published in a peer-reviewed journal, (b) reporting a relation between the SNP rs6265 and sMRI, (c) showing hippocampal data. A total of 27 publications met these criteria, whereof from one recent genome-wide association study (GWAS) data of 5 cohorts were obtained (Stein et al., 2012). Altogether a total

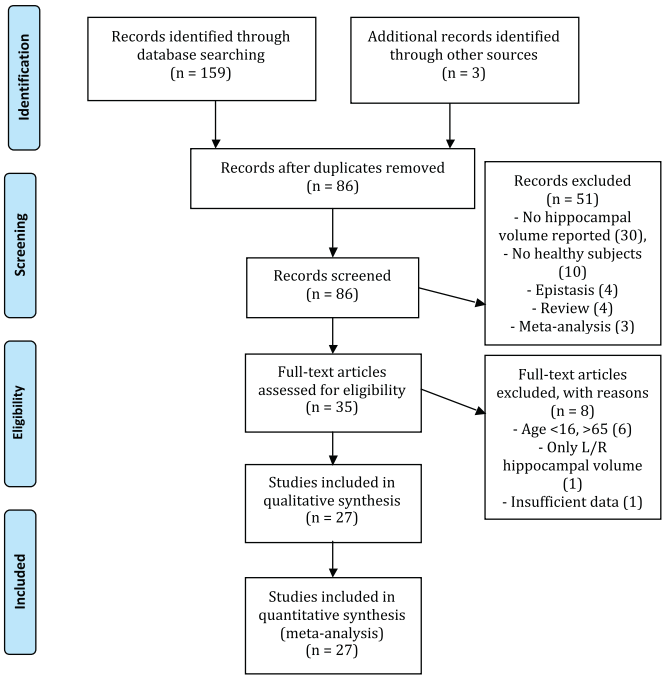

Fig. 1. Flow chart of the search strategy and included studies for meta-analysis.

of 32 samples, 31 previously published and our own data, were included in this meta-analysis. Criteria for exclusion were: mean age of participants (<15 or >65 years), not clearly defined healthy control group, overlapping datasets, and only left or only right hippocampal volume reported. The authors were contacted when information essential for the calculation of effect sizes was missing. Both measuring techniques, i.e. automated and manual tracing, were included. We followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher et al., 2010).

2.2.2. Data extraction

The following variables were extracted: First author name, publication year, number of independent samples per study. For each independent sample, we extracted sample size of genotype subgroups, ethnicity, gender, mean age of sample, Hardy–Weinberg equilibrium (HWE; calculated, when not reported), genotyping method, structural MRI measurement technique, direction of effect, field strength of MR scanner, mean hippocampal volumes and standard deviation, *t*-statistic, *F*-statistic and *p*-values per genotype, and whether the hippocampal volumes were normalized to ICV. To sustain statistical independence, one single effect size per sample was used for this meta-analysis.

2.2.3. Quality assessment

Using an 11-item checklist adapted from (Karg et al., 2011) the quality of the included studies was evaluated. In detail, the criteria were: (1) Funding – role in analysis and interpretation of data, (2) Sample size, (3) Clear inclusion criteria for participants, (4) Reported allele distribution, (5) Ethnicity assessed, (6) If mixed ethnicity: discussion of problems, (7) IQ/educational level available, (8) Inter- and intrarater reliability, (9) Report of HWE, (10) Sample in HWE and (11) Additional descriptive data including age, gender, genotyping method, magnetic field strength of scanner. For each category 0, 1 or 2 points were given. Finally, the included studies were rated according to the sum of the points and characterized as high (above 80% of the maximal sum of points), moderately high (60–79%), moderate (40–59%), moderately low (20–39%), and low quality studies (below 19%) (for more details see supplementary tables S1 and S2).

2.2.4. Data analysis

Data were entered into an electronic database and quantitative meta-analysis was performed using the R 2.15.2 software (R Core Team, 2012). The effect size was calculated using Hedge's *g*, which provides an unbiased standardized mean difference that incorporates a correction for small sample sizes (Lipsey and Wilson, 2000). Hedge's g values above 0.2, 0.5 and 0.8 correspond to small, medium and large effect sizes respectively. Hedge's g was calculated using data of mean hippocampal volumes, standard deviations and sample sizes. Where these data were not available, we employed the *t*-statistic, *F*-statistic or *p*-values, together with the corresponding sample sizes. A positive value of the effect size reflected larger hippocampal volumes in the Val/Val homozygotes than for the Met-carriers of the SNP rs6265. We employed a random-effects model with the DerSimonian-Laird estimator using the metafor package (DerSimonian and Laird, 1986; Wolfgang Viechtbauer, 2010). The random-effects model shows more flexibility with respect to effect size variability between studies and study populations (Cooper et al., 2009), as it incorporates the between-study variance τ^2. And in case of high between-study heterogeneity, the random-effects model compared to the fixed-effects model is the model of choice (Ioannidis et al., 2007).

Cochran's *Q* test was then used to calculate between-group heterogeneity; the magnitude of heterogeneity was assessed by I^2 (Higgins and Thompson, 2002). I^2 is an estimate of variability across studies based on heterogeneity rather than chance, ranging from 0 to 100%. Values above 25%, 50% and 75% corresponded to low, moderate and high heterogeneity respectively (Higgins and Thompson, 2002). Furthermore, potential publication bias was investigated by funnel plot asymmetry and Egger's regression test (Egger et al., 1997). In case of a bias, "the trim and fill" method was used subsequently to identify and correct for publication bias detected by an asymmetric funnel plot (Duval and Tweedie, 2000). A series of meta-regression analyses was carried out to assess the impact of possibly moderating study design characteristics such as publication year, age of participants, gender ratio, ethnicity, Val/Met ratio, sample size, quality rating, magnetic field strength, hippocampal volumes normalized to intracranial volume and applied hippocampal measuring techniques. Most studies used a dominant allele approach, but two studies reported an additive allele comparison (Agartz et al., 2006; Gruber et al., 2012). Nevertheless, these were treated equivalently in this analysis.

3. Results

3.1. Association analysis of 643 healthy subjects

Of the 643 subjects, 413 were homozygous for the Val allele, 204 were heterozygous Val/Met, and 26 were homozygous for Met allele. Met-carriers were taken together in a single group. Genotype groups did not differ according to age, sex, profession and handedness (see Table 1). All 643 subjects had complete genotype information. The genotype distribution did not deviate from the Hardy–Weinberg equilibrium ($p = 0.90$).

As shown in Fig. 2, there were no significant genotype-dependent differences in the z-transformed scores of the left (Val/Val homozygous 0.029 ± 0.97 ($n = 413$), Met-carriers 0.001 ± 0.98 ($n = 230$); $p = 0.25$, see Fig. 2), right (Val/Val homozygous 0.048 ± 0.96 ($n = 413$), Met-carriers 0.043 ± 1.05 ($n = 230$); $p = 0.12$, see Fig. 2) and mean hippocampal volume (Val/Val homozygous 0.041 ± 0.97 ($n = 413$), Met-carriers 0.023 ± 1.01 ($n = 230$); $p = 0.15$, see Fig. 2). The difference between genotypes in mean hippocampal volumes resulted in a non-significant *g* of 0.05 ($p = 0.58$). We did not observe a main effect of age or sex as well as no

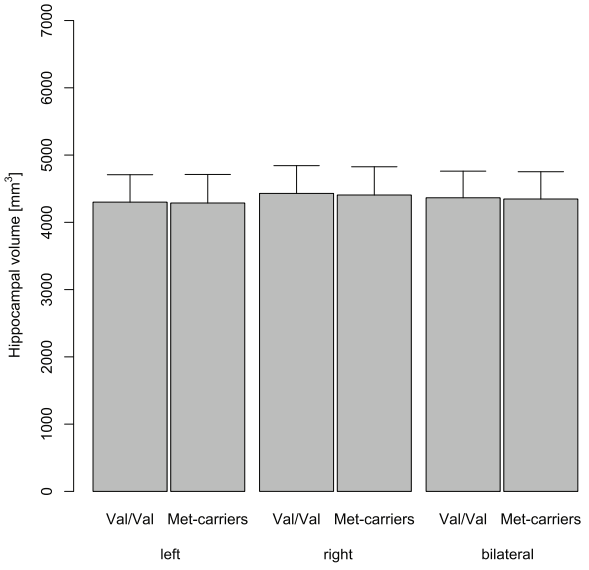

Fig. 2. Barplot showing left, right and mean bilateral hippocampal volumes [mm^3] ± standard deviation of our original data. Neither the left, right nor mean bilateral hippocampus showed a significant difference between 230 Met-carriers and 413 Val/Val homozygotes.

interaction effect of sex and rs6265 genotype groups on hippocampal volumes (see supplementary methods and supplementary table S3).

3.2. Description of studies and cohorts included in the meta-analysis

A total of 4655 subjects in 32 datasets were selected for this random-effects meta-analysis (Agartz et al., 2006; Bueller et al., 2006; Cerasa et al., 2010; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gatt et al., 2009; Gonul et al., 2011; Gruber et al., 2012; Jessen et al., 2009; Joffe et al., 2009; Koolschijn et al., 2010; Molendijk et al., 2012b; Montag et al., 2009; Nemoto et al., 2006; Pezawas et al., 2004; Richter-Schmidinger et al., 2011; Sanchez et al., 2011; Schofield et al., 2009; Smith et al., 2012; Soliman et al., 2010; Stein et al., 2012; Stern et al., 2008; Szeszko et al., 2005; Takahashi et al., 2008; Yang et al., 2012). All 27 included studies were published between 2004 and 2012. This structural MRI meta-analysis comprises 1771 Met-carriers and 2884 Val/Val homozygotes. For an overview of all included samples, see Table 2. Ethnicity was reported in 26 samples, of which 19 were performed on a Caucasian sample, 2 on a Japanese sample, 1 on a Chinese sample and 4 on a sample of mixed ethnicity. The overall mean age of all datasets providing this information was 31.65 ± 9.0. The Hardy–Weinberg equilibrium did not deviate in 28 datasets, whereas in 3 datasets this parameter could not be calculated due to insufficient data. Quality analysis showed that most of the included studies were of high or moderate quality (44% high and 48% moderate scores, supplementary table S1 and table S2).

3.3. Meta-analysis of one original and 31 previously published samples

Meta-analysis of all datasets ($k = 32$) showed evidence for significant, albeit weak association between hippocampal volumes and SNP rs6265 ($g = 0.09$, se = 0.04, 95% CI = [0.01–0.17], $Z = 2.08$, $p = 0.0376$, see Fig. 3A and table S4), with indications of significant between-study heterogeneity ($I^2 = 38.24\%$, Q(df = 31) = 50.20, $p = 0.02$). The effect was in the direction of slightly smaller hippocampal volumes for Met-carriers than for Val/Val homozygotes. Visual inspection of the funnel plot indicated evidence for potential publication bias (Fig. 3B, table S4). This was quantitatively confirmed by significant regression intercept in Egger's regression test ($p = 0.0075$). The trim and fill procedure suggested 8 missing studies on the left side of the funnel plot and a corrected non-significant Hedge's g of 0.02 (95% CI = [−0.07–0.11], Fig. 3B). Meta-regression analysis did not reveal any effect for age of participants ($\beta = -0.08$, $F(1,30) = 0.18$, $p = 0.67$), gender ratio ($\beta = 0.13$, $F(1,30) = 0.48$, $p = 0.49$), ethnicity of the subjects ($\beta = 0.26$, $F(1,25) = 1.83$, $p = 0.19$), Val/Met ratio ($\beta = 0.14$, $F(1,24) = 0.48$, $p = 0.50$), sample size ($\beta = -0.23$, $F(1,30) = 1.71$, $p = 0.20$), quality rating ($\beta = -0.32$, $F(1,24) = 2.74$, $p = 0.11$), magnetic field strength ($\beta = -0.22$, $F(1,28) = 1.49$, $p = 0.23$), or hippocampal volumes normalized to ICV ($\beta = -0.01$, $F(1,30) = 0.002$, $p = 0.96$). However, the analysis of the meta-regressions indicated a potential source for bias related to measurement techniques ($\beta = 0.43$, $F(1,29) = 6.55$, $p = 0.02$) (see Fig. 3C and table S4) and year of publication ($\beta = -0.38$, $F(1,30) = 5.01$, $p = 0.03$) (see Fig. 3A, cumulative meta-analysis, and table S4).

3.4. Effect of moderators

To further disentangle the moderating effect of the measurement technique, samples were subsequently subdivided into manually and automatically segmented volumes of the hippocampi. One study using semi-automated analysis was excluded from further analysis (Sanchez et al., 2011), leaving 13 samples with manual tracing ($n = 829$ subjects) and 18 samples using automated segmentation ($n = 4426$ subjects). The detected small effect size estimate of manual tracing samples indicated significantly smaller hippocampal volumes for Met-carriers compared to Val/Val subjects ($g = 0.22$, se = 0.09, 95% CI = [0.05–0.39], $Z = 2.51$, $p = 0.0121$, $I^2 = 38.12\%$, $Q(\mathrm{df} = 12) = 19.39$, $p = 0.08$, Trim and fill: 5 missing studies on left side of the funnel plot and a corrected non-significant g of 0.08, see Fig. 4A and table S4). The meta-analysis of the manual tracing samples revealed significant publication bias (Egger's test: $z = 3.24$, $p = 0.0012$), significant between-study heterogeneity and a significant moderator effect only for the sample size ($\beta = -0.72$, $F(1,11) = 12.07$, $p = 0.01$). Analysis of the relation between years of publication and effect size revealed a significant decrease in the effect sizes with increasing sample size over the years, but only for manual tracing samples (see Fig. 5). In contrast, the overall effect size of the samples using automatic measurement techniques showed no significant genotype effect ($g = 0.04$, se = 0.05, 95% CI = [−0.05–0.13], $Z = 0.89$, $p = 0.3751$, $I^2 = 37.87\%$, $Q(\mathrm{df} = 17) = 27.36$, $p = 0.05$, see Fig. 4B and table S4).

4. Discussion

In this paper, we present a joint analysis of the relation between the BDNF SNP rs6265 and the hippocampal volumes in healthy young subjects. Specifically, we first explored whether hippocampal volumes of 643 healthy individuals differed between Val/Val homozygotes and Met-carriers. These data were further incorporated into a meta-analysis of previously published studies subsuming a total of 5298 healthy subjects.

Hippocampal volume is a heritable quantitative trait (estimates vary between 40 and 69%). Hence, several studies have analyzed the association between candidate genes, such as BDNF, and the hippocampus (Goldman et al., 2008; Peper et al., 2007; Sullivan et al., 2001). However, the studies investigating the association between BDNF SNP rs6265 and hippocampal volumes report inconsistent findings. Some studies observe BDNF-dependent differences in hippocampal volumes (Bueller et al., 2006; Montag et al., 2009; Pezawas et al., 2004; Schofield et al., 2009), whereas others do not find an association (Agartz et al., 2006; Cerasa et al., 2010; Chepenik et al., 2009; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gatt et al., 2009; Gruber et al., 2012; Jessen et al., 2009; Joffe et al., 2009; Koolschijn et al., 2010; Molendijk et al., 2012b; Nemoto et al., 2006; Richter-Schmidinger et al., 2011; Sanchez et al., 2011; Smith et al., 2012; Soliman et al., 2010; Stein et al., 2012; Stern et al., 2008; Szeszko et al., 2005; Takahashi et al., 2008; Yang et al., 2012). The results based on our own data as well as the meta-analysis across studies applying automatic hippocampal segmentation do not support an association between rs6265 and hippocampal volumes.

Several studies report BDNF-dependent volume differences in the hippocampus of patients with neuropsychiatric disorders such as bipolar disorder and schizophrenia (Chepenik et al., 2009; Szeszko et al., 2005) as well as between healthy controls and patients of the same genotype (Chepenik et al., 2009; Gonul et al., 2011; Koolschijn et al., 2010; Smith et al., 2012). Other studies in patient populations found no association of the rs6265 polymorphism and hippocampal volumes (Agartz et al., 2006; Cerasa et al., 2010; Cole et al., 2011; Dutt et al., 2009; Frodl et al., 2007; Gruber et al., 2012; Jessen et al., 2009; Molendijk et al., 2012b; Takahashi et al., 2008). Two recent meta-analyses did not find a significant association of SNP rs6265 and hippocampal structure in neuropsychiatric disorders, including schizophrenia, bipolar disorder, depressive and anxiety disorders (Kambeitz et al., 2012; Molendijk et al., 2012a). However, the meta-analyses were not conducted separately per psychiatric disease category and treatment

Table 2
Overview of included imaging genetics samples.

Author	Year	*n*	Age [mean ± SD]	Females/ males	Met/Met	Val/Met or Met-carriers	Val/Val	HWE	Genotyping method	Norm. to ICV	Magnet field strength	Direction of effect	Hippocampal measuring technique
Agartz et al. (Agartz et al., 2006)	2006	104	41.6 ± 8.9	35/69	4	27	73	y°	Pyrosequencing	+	1.5 T	Met/Met < Val/Met < Val/Val	Manual tracing
Bueller et al. (Bueller et al., 2006)	2006	36	27.1 ± 6.6	22/14	0	15	21	y°	PCR-RFLP	+	1.5 T	Met/Val < Val/Val	Manual tracing
Cerasa et al. (Cerasa et al., 2010)	2010	139	36.0 ± 13.4	82/57	7	51	81	y°	PCR-RFLP	–	1.5 T	Met-carriers < Val/Val	SPM99: ROI
Chepenik et al. (Chepenik et al., 2009)	2009	18	28 ± 12	12/6	0	6	12	y°	TaqMan	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Cole et al. (Cole et al., 2011)	2011	109	33.0 ± 9.2	54/55	4	37	68	y	PCR-RFLP or TaqMan	+	1.5 T	Met-carriers > Val/Val	Manual tracing
Dutt et al. (Dutt et al., 2009)	2009	60	40.8 ± 15.1	33/28	–	17	43	y	SNuPe technology	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Frodl et al. (Frodl et al., 2007)	2007	60	41.6 ± 12.3	29/31	1	19	40	y	RT-PCR	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Gatt et al. (Gatt et al., 2009)	2009	89	36.2 ± 12.7	28/61	–	26	63	y	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	SPM2: VBM: ROI
Gonul et al. (Gonul et al., 2011)	2011	40	29.8 ± 6.4	17/23	0	16	24	y	RT-PCR	–	1.5 T	Met-carriers < Val/Val	Manual tracing
Gruber et al. (Gruber et al., 2012)	2012	39	38.2 ± 12.8 *	49/57 *	3	12	24	y	PCR-RFLP	+	1.5 T	Met/Met > Val/Met > Val/Val	Manual tracing
Jessen et al. (Jessen et al., 2009)	2009	84	43.9 ± 8.7	40/44	–	29	55	?	TaqMan	–	1.5 T and 3 T	Met-carriers < Val/Val	Manual tracing
Joffe et al. (Joffe et al., 2009)	2009	113	36.8 ± 13.1 *	224/243 *	2	43	68	y	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	SPM2: VBM: ROI
Koolschijn et al. (Koolschijn et al., 2010)	2010	90	38.2 ± 13.6	34/56	5	26	59	y	Illumina Bead Array	–	1.5 T	Met-carriers > Val/Val	Manual tracing
Millan Sanchez et al. (Sanchez et al., 2011)	2011	43	57.0 ± 0.9 *	22/122 *	–	19	24	?	Illumina Bead Array	–	1.5 T	Met-carriers > Val/Val	Surgical Navigation Technologies
Molendijk et al. (Molendijk et al., 2012b)	2012	31	37.4 ± 10.1 *	100/57 *	0	10	21	y°	Four genotyping array	–	3.0 T	Met/Val < Val/Val	SPM5: VBM: ROI
Montag et al. (Montag et al., 2009)	2009	87	23.9 ± 4.8	63/24	6	27	54	y	RT-PCR	+	1.5 T	Met-carriers < Val/Val	SPM5: VBM: ROI
Nemoto et al. (Nemoto et al., 2006)	2006	109	36.2 ± 12.1	71/38	17	51	41	y	TaqMan	–	1.5 T	Met-carriers < Val/Val	SPM2: VBM: ROI
Pezawas et al. (Pezawas et al., 2004)	2004	111	32.6 ± 9.3	55/56	–	42	69	?	Genotyped	+	1.5 T	Met-carriers < Val/Val	SPM2: VBM: ROI
Richter-Schmidinger et al. (Richter-Schmidinger et al., 2011)	2011	135	24.6 ± 3.2	91/44	11	40	84	y°	PCR-RFLP	–	1.5 T	Met-carriers > Val/Val	Manual tracing

Table 2 (*Continued*)

Author	Year	*n*	Age [mean ± SD]	Females/ males	Met/Met	Val/Met or Met-carriers	Val/Val	HWE	Genotyping method	Norm. to ICV	Magnet field strength	Direction of effect	Hippocampal measuring technique
Schofield et al. (Schofield et al., 2009)	2009	161	32.6 ± 13	75/106	6	59	96	y	PCR-RFLP	–	1.5 T	Met-carriers < Val/Val	SPM2: VBM: whole brain
Smith et al. (Smith et al., 2012)	2012	39	21.2 ± 4.6	19/20	8	10	21	y	TaqMan	–	1.5 T	Met-carriers < Val/Val	FreeSurfer: ROI
Soliman et al. (Soliman et al., 2010)	2010	70	24.9 ± 4.6	34/36	3	32	35	y°	TaqMan	+	3.0 T	Met-carriers > Val/Val	FreeSurfer: ROI
Stern et al. (Stern et al., 2008)	2008	50	31.7 ± 10.5	17/33	0	12	38	y°	TaqMan	+	3.0 T	Met/Val < Val/Val	FreeSurfer: ROI
Szeszko et al. (Szeszko et al., 2005)	2005	25	27.1 ± 6.7	15/10	0	10	15	y	TaqMan	+	1.5 T	Met/Val < Val/Val	Manual tracing
Takahashi et al. (Takahashi et al., 2008)	2008	29	24.2 ± 6.1	12/17	5	11	13	y	PCR-RFLP	+	1.5 T	Met-carriers < Val/Val	Manual tracing
Yang et al. (Yang et al., 2012)	2012	61	20.5 ± 0.9 *	27/34	17	29	15	y	PCR-Sequencing	–	3.0 T	Met-carriers < Val/Val	FSL-VBM
BFS cohort (Stein et al., 2012)	2012	220	24.0 ± 7.7	115/105	6	82	132	y	Illumina Omni Express	–	1.5 T	Met-carriers > Val/Val	FSL FIRST
BIG cohort (Stein et al., 2012)	2012	1281	22.8 ± 3.3 *	735/546	62	411	808	y	Affymetrix microarray	–	1.5 T and 3 T	Met-carriers > Val/Val	FSL FIRST
MooDS cohort (Stein et al., 2012)	2012	221	33.1 ± 10.0	119/102	–	81	140	y	Illumina Human610-Quad	–	3.0 T	Met-carriers > Val/Val	FreeSurfer
TOP cohort (Stein et al., 2012)	2012	190	35.8 ± 9.7	91/99	8	55	127	y	Affymetrix Human SNP 6.0	–	1.5 T	Met-carriers > Val/Val	FreeSurfer
QTIM cohort (Stein et al., 2012)	2012	811	23.1 ± 2.8	506/305	37	254	520	y	Illumina 610 K	–	4.0 T	Met-carriers < Val/Val	FSL FIRST

HWE, Hardy–Weinberg equilibrium; ICV, intracranial volume; Met, methionine, ROI, region of interest; Val, valine; VBM, voxel-based morphometry; association study cohorts included in Stein et al. (34): BFS, Bipolar Family Study; BIG, Brain Imaging Genetic Study; MooDS, Mood Disorders and Schizophrenia; TOP, Thematically Organized Psychosis Study; QTIM, Queensland Twin Imaging Measures; *, reported of larger sample only; ?, not possible to calculate;°, calculated of raw data.

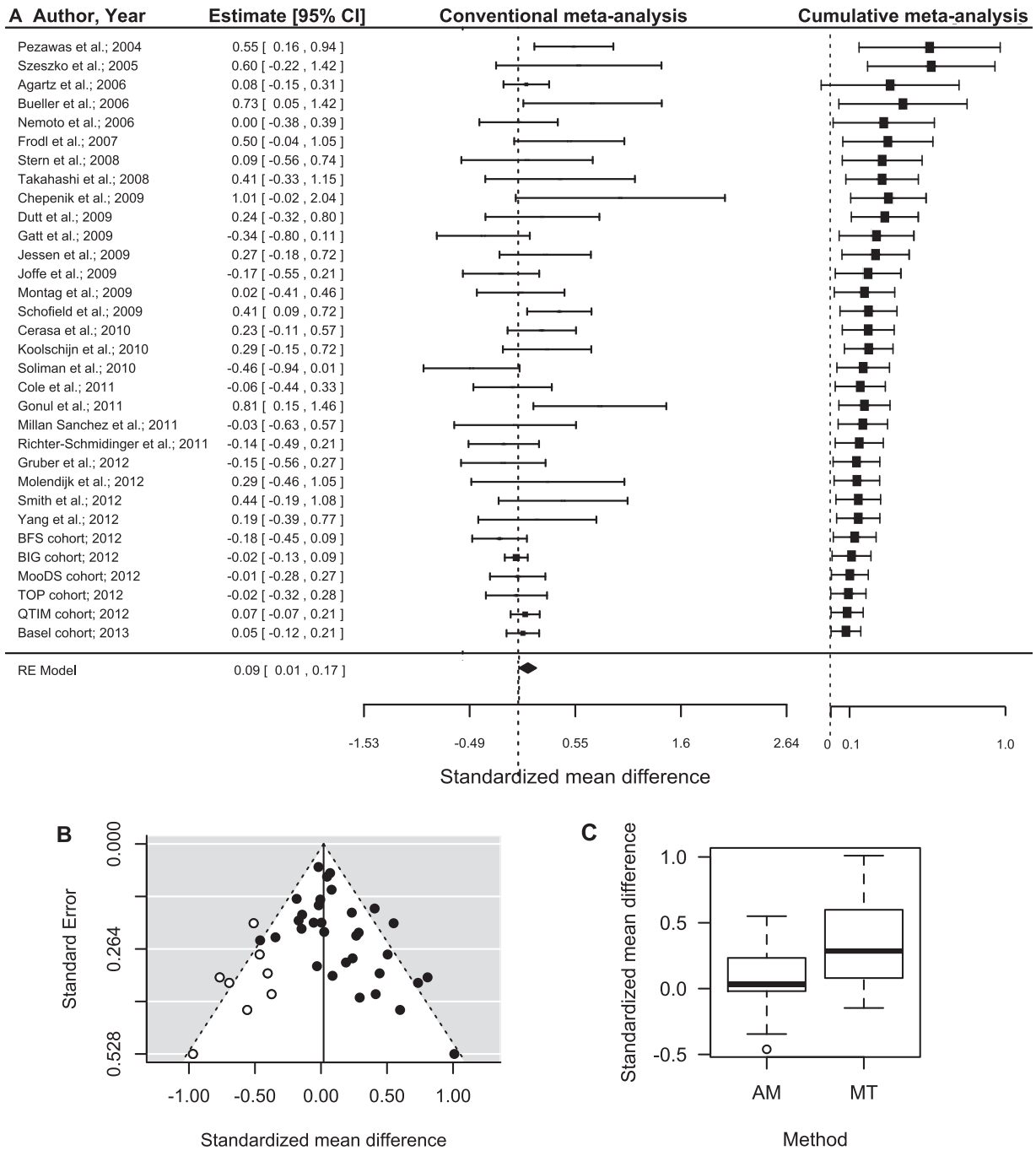

Fig. 3. (A) Forest plots of random-effects meta-analysis assessing hippocampal volumes with structural MRI and the BDNF SNP rs6265. Positive effect sizes indicate larger hippocampi in the Val allele subjects than with the Met allele subjects. The forest plot of a cumulative meta-analysis shows the change of the evidence over time. Dashed lines indicate zero line. (B) Funnel plot with additional trim and fill procedure where white dots indicate the missing studies to correct for potential publication bias. (C) Meta-regression analysis of the hippocampal measuring technique and the effect of the SNP rs6265, MT: manual tracing, AM: automatic measurement.

effects may have influenced the hippocampal volumes (Fusar-Poli et al., 2013).

Inconsistent findings in studies of healthy subjects and psychiatric patients raise the question if BDNF-dependent structural hippocampal differences are specific for different developmental stages. Until now, only few studies have addressed this issue by investigating the relationship between BDNF and hippocampal volumes in neonates, children and adolescents and also elderly. Two studies have not observed BDNF-dependent differences in hippocampal volumes in children and adolescents (age range 8–19) (Mueller et al., 2013; Toro et al., 2009). In contrast, Knickmeyer and colleagues find rs6265-dependent differences in hippocampal volumes in neonates (Knickmeyer et al., 2013). However, in order to investigate the influence of developmental stages on BDNF-dependent effects, additional longitudinal studies will be necessary. For instance, Knickmeyer and colleagues will implement a follow-up design, collecting data over several time points (at age 1, 2, 4 and 6 years of age) (Knickmeyer et al., 2013). Moreover, several studies report hippocampal volume reductions in aging (Driscoll et al., 2003; Erickson et al., 2010; Malykhin et al., 2008; Raz et al., 2010). Erikson and colleagues investigated the relationship between serum BDNF levels, age, hippocampal volume and

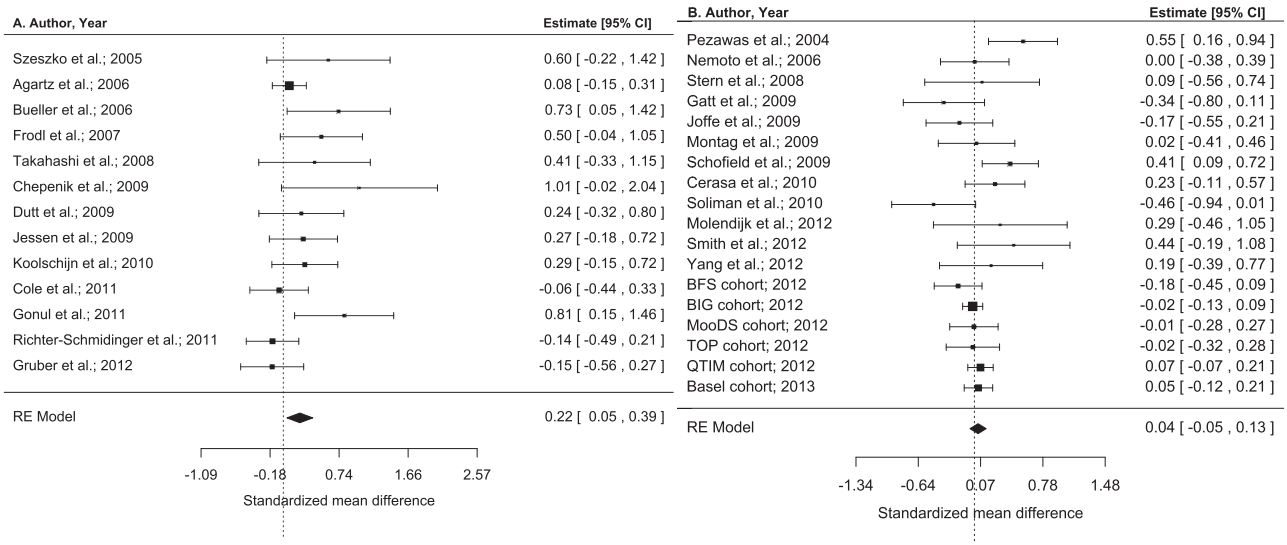

Fig. 4. Forest plots of BDNF SNP rs6265 of structural MRI studies assessing potential publication bias arising from the applied hippocampus analysis technique. (A) Manual traced hippocampus; (B) Hippocampus volumes evaluated by automatic measurement; positive effect sizes indicate larger hippocampi in the Val allele subjects compared to the Met-carriers. Dashed lines indicate zero line.

memory performance (Erickson et al., 2010). Age was associated with reduced hippocampal volumes as well as reduced BDNF serum levels and poorer memory performance. In his review, Von Bohlen und Halbach suggests a role of BDNF in age-dependent processes in the hippocampus (Von Bohlen und Halbach, 2010). However, studies investigating the association of rs6265 with hippocampal volumes in also aged populations report inconsistent results (Brooks et al., 2014; Karnik et al., 2010; Sanchez et al., 2011).

The importance of the hippocampus in learning and memory is well established (Squire and Wixted, 2011) and it has been suggested that BDNF plays a role in these processes (Baj et al., 2013; Cunha et al., 2010). Even though we did not find BDNF-dependent differences in hippocampal volumes, the absence of difference on the anatomical level does not rule out that BDNF modulates other processes in the hippocampus. Indeed, two studies included in this meta-analysis provide support for BDNF-dependent differences in hippocampal activation during memory paradigms in the absence of structural differences (Cerasa et al., 2010; Molendijk et al., 2012b), which is further supported by additional studies analyzing functional MRI data (Dennis et al., 2011; Egan et al., 2003; Hariri et al., 2003; Hashimoto et al., 2008). However, the meta-analysis by Kambeitz and colleagues did not find an association between rs6265 and hippocampus-mediated memory activation, which might be explained by the large variety of paradigms combining working and episodic memory processes (Kambeitz et al., 2012). Moreover, meta-analyses assessing an association between rs6265 and declarative memory performance revealed contradictory results (Kambeitz et al., 2012; Mandelman and Grigorenko, 2012).

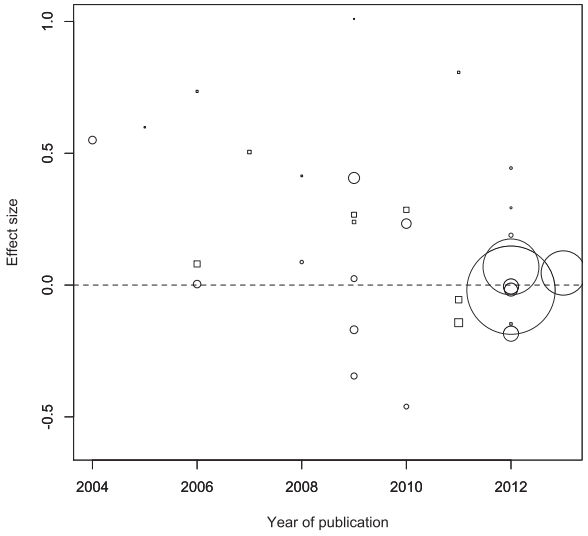

Fig. 5. Scatter plot showing the relation between effect size and year of publication for the association of the hippocampal volume and BDNF SNP rs6265. The size of the shapes indicates the sample size of each study. Squares represent the studies that traced the hippocampus manually; circles represent the studies that measured the hippocampus automatically. Dashed line indicates zero line.

In our meta-analysis we observed an effect of the applied measuring technique (manually traced vs. automatically measured hippocampal volumes) after we investigated the effect of several moderators due to significant between-study heterogeneity and publication bias. First, the overall meta-analysis showed a weakly ($g = 0.09$) significant association between hippocampal volumes and SNP rs6265. In particular, Val/Val homozygotes had significantly larger hippocampal volumes than Met-carriers. The direction of the effect is in accordance with recent meta-analyses of healthy subjects (Hajek et al., 2012; Kambeitz et al., 2012; Molendijk et al., 2012a), but the effect size in this study was considerably smaller. To further disentangle the dissociable effect of these two measurement approaches, subsequent analyses were conducted after separating the samples by the hippocampus measuring technique. We found that Met-carriers had smaller hippocampal volumes than Val/Val homozygotes ($g = 0.22$) when the hippocampi were manually segmented. In contrast, we did not find a significant genotype effect with automatic segmentation ($g = 0.04$). This latter result is consistent with the findings of our original sample in 643 healthy subjects, where we used the automatic segmentation technique from FreeSurfer and also with the results of a recent GWAS analysis in 5776 healthy subjects (Stein et al., 2012). Even though manual segmentation is generally considered as the gold standard due to the precise delineation of anatomical structures, the increasing sample size of imaging studies renders the process of manual segmentation less practicable, as it is both costly and time consuming. Several studies compared manual and different automatic segmentation methods and report comparable accuracy, sensitivity and reproducibility (Bergouignan et al., 2009; De Boer et al., 2010; Doring et al., 2011; Morey et al., 2009).

Specifically, automated segmentation of the hippocampus using FreeSurfer shows higher correlations with manual segmentation compared to FSL/First (Doring et al., 2011; Morey et al., 2009). Nonetheless, it has been shown that, compared to manual segmentation, FreeSurfer and FSL overestimate hippocampal volumes (Doring et al., 2011; Morey et al., 2009) while they are underestimated by SACHA (Bergouignan et al., 2009). However, our meta-analysis across studies using only manual tracing samples revealed a publication bias, between-study heterogeneity and a moderator effect for the sample size. These effects were further studied in detail to investigate the relation between sample size and publication year. We showed that effect sizes shrink as a function of publication year and sample size. In contrast to the findings of previous meta-analyses (Kambeitz et al., 2012; Molendijk et al., 2012a), this decrease in effect size could not be attributed to publication year alone, but was also linked to an increase in sample size.

Several limitations of our analyses need to be considered. In our meta-analysis, we could not address laterality differences or differences in specific hippocampal sub-regions as many of the included studies only report total hippocampal volumes. Furthermore, we explicitly focused on the impact of the rs6265 polymorphism on hippocampal volumes in healthy subjects, without considering the effect of other SNPs, gene-gene interactions (Honea et al., 2009) or gene-environment interactions (Gatt et al., 2009; Gerritsen et al., 2012). This is of particular relevance, as the impact of the BDNF SNP rs6265 on hippocampal volume could be modified by other SNPs that have already been shown to impact the volume of the hippocampus, such as the Val159Met polymorphism of catecholamine-O-methyltransferase (COMT) (Cerasa et al., 2008; Dutt et al., 2009; Ehrlich et al., 2010; Honea et al., 2009; Taylor et al., 2007), an SNP of ZNF804a (Donohoe et al., 2011; Wei et al., 2012) or the intergenic variant rs7294919 (Stein et al., 2012). Finally, we did not observe a main effect of sex and age on hippocampal volumes, nor did we observe an interaction effect of sex and genotype on hippocampal volumes. Other studies found sex- (Cahill, 2006; Goldstein et al., 2001; Liu et al., 2010; Ruigrok et al., 2013), and age-dependent differences in hippocampal volumes (Driscoll et al., 2003; Malykhin et al., 2008; Raz et al., 2010). Since the association of rs6265 and age-dependent hippocampal changes revealed controversial results (Brooks et al., 2014; Karnik et al., 2010; Sanchez et al., 2011) and the role of sex in this association is not well understood, it would be interesting if future studies would address these questions. Potential reasons for the absence of such effects in our original study are the applied correction for intracranial volume and the limited age-range of our sample.

In summary, the present study does not support the association between SNP rs6265 and hippocampal volumes in healthy individuals. The weak effect observed in the meta-analysis is mainly driven by studies with small sample sizes applying manual segmentation of hippocampi. Our findings confirm the results of previous results based on a large sample size. Moreover, our findings demonstrate an effect of measuring techniques, publication year and sample size.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.03.011.

References

Agartz, I., Sedvall, G.C., Terenius, L., Kulle, B., Frigessi, A., Hall, H., Jönsson, E.G., 2006. BDNF gene variants and brain morphology in schizophrenia. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 141B, 513–523.

Baj, G., Carlino, D., Gardossi, L., Tongiorgi, E., 2013. Toward a unified biological hypothesis for the BDNF Val66Met-associated memory deficits in humans: a model of impaired dendritic mRNA trafficking. Front. Neurosci. 7, 188.

Barde, Y.A., Edgar, D., Thoenen, H., 1982. Purification of a new neurotrophic factor from mammalian brain. EMBO J. 1, 549–553.

Bellenguez, C., Strange, A., Freeman, C., Donnelly, P., Spencer, C.C.A., Wellcome Trust Case Control Consortium, 2012. A robust clustering algorithm for identifying problematic samples in genome-wide association studies. Bioinformatics 28, 134–135.

Bergouignan, L., Chupin, M., Czechowska, Y., Kinkingnéhun, S., Lemogne, C., Le Bastard, G., Lepage, M., Garnero, L., Colliot, O., Fossati, P., 2009. Can voxel based morphometry, manual segmentation and automated segmentation equally detect hippocampal volume differences in acute depression? Neuroimage 45, 29–37.

Boulle, F., van den Hove, D.L.A., Jakob, S.B., Rutten, B.P., Hamon, M., van Os, J., Lesch, K.-P., Lanfumey, L., Steinbusch, H.W., Kenis, G., 2012. Epigenetic regulation of the BDNF gene: implications for psychiatric disorders. Mol. Psychiatry 17, 584–596.

Brandys, M.K., Kas, M.J.H., van Elburg, A.A., Ophoff, R., Slof-Op't Landt, M.C.T., Middeldorp, C.M., Boomsma, D.I., van Furth, E.F., Slagboom, P.E., Adan, R.A.H., 2011. The Val66Met polymorphism of the BDNF gene in anorexia nervosa: new data and a meta-analysis. World J. Biol. Psychiatry, 1–11.

Brooks, S.J., Nilsson, E.K., Jacobsson, J.A., Stein, D.J., Fredriksson, R., Lind, L., Schiöth, H.B., 2014. BDNF polymorphisms are linked to poorer working memory performance, reduced cerebellar and hippocampal volumes and differences in prefrontal cortex in a Swedish elderly population. PLoS ONE 9, e82707.

Bueller, J.A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., Zubieta, J.-K., 2006. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol. Psychiatry 59, 812–815.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477–484.

Cerasa, A., Gioia, M.C., Labate, A., Liguori, M., Lanza, P., Quattrone, A., 2008. Impact of catechol-O-methyltransferase Val(108/158) Met genotype on hippocampal and prefrontal gray matter volume. Neuroreport 19, 405–408.

Cerasa, A., Tongiorgi, E., Fera, F., Gioia, M.C., Valentino, P., Liguori, M., Manna, I., Zito, G., Passamonti, L., Nisticò, R., Quattrone, A., 2010. The effects of BDNF Val66Met polymorphism on brain function in controls and patients with multiple sclerosis: an imaging genetic study. Behav. Brain Res. 207, 377–386.

Chen, Z.-Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.-J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic Variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 314, 140–143.

Chen, Z.-Y., Patel, P.D., Sant, G., Meng, C.-X., Teng, K.K., Hempstead, B.L., Lee, F.S., 2004. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J. Neurosci. 24, 4401–4411.

Chepenik, L.G., Fredericks, C., Papademetris, X., Spencer, L., Lacadie, C., Wang, F., Pittman, B., Duncan, J.S., Staib, L.H., Duman, R.S., Gelernter, J., Blumberg, H.P., 2009. Effects of the brain-derived neurotrophic growth factor val66met variation on hippocampus morphology in bipolar disorder. Neuropsychopharmacology 34, 944–951.

Cole, J., Weinberger, D.R., Mattay, V.S., Cheng, X., Toga, A.W., Thompson, P.M., Powell-Smith, G., Cohen-Woods, S., Simmons, A., McGuffin, P., Fu, C.H.Y., 2011. No effect of 5HTTLPR or BDNF Val66Met polymorphism on hippocampal morphology in major depression. Genes Brain Behav. 10, 756–764.

Cooper, H., Hedges, L.V., Valentine, J.C., 2009. The Handbook of Research Synthesis and Meta-analysis, 2nd ed. Russell Sage Foundation, New York, NY, US.

Cunha, C., Brambilla, R., Thomas, K.L., 2010. A simple role for BDNF in learning and memory? Front. Mol. Neurosci. 3, 1.

De Boer, R., Vrooman, H.A., Ikram, M.A., Vernooij, M.W., Breteler, M.M.B., van der Lugt, A., Niessen, W.J., 2010. Accuracy and reproducibility study of automatic MRI brain tissue segmentation methods. Neuroimage 51, 1047–1056.

De Quervain, D.J.-F., Papassotiropoulos, A., 2006. Identification of a genetic cluster influencing memory performance and hippocampal activity in humans. Proc. Natl. Acad. Sci. U. S. A. 103, 4270–4274.

Dennis, N.A., Cabeza, R., Need, A.C., Waters-Metenier, S., Goldstein, D.B., LaBar, K.S., 2011. Brain-derived neurotrophic factor val66met polymorphism and hippocampal activation during episodic encoding and retrieval tasks. Hippocampus 21, 980–989.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An

automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.
Donohoe, G., Rose, E., Frodl, T., Morris, D., Spoletini, I., Adriano, F., Bernardini, S., Caltagirone, C., Bossù, P., Gill, M., Corvin, A.P., Spalletta, G., 2011. ZNF804A risk allele is associated with relatively intact gray matter volume in patients with schizophrenia. Neuroimage 54, 2132–2137.
Doring, T.M., Kubo, T.T.A., Cruz Jr., L.C.H., Juruena, M.F., Fainberg, J., Domingues, R.C., Gasparetto, E.L., 2011. Evaluation of hippocampal volume based on MR imaging in patients with bipolar affective disorder applying manual and automatic segmentation techniques. J. Magn. Reson. Imaging 33, 565–572.
Driscoll, I., Hamilton, D.A., Petropoulos, H., Yeo, R.A., Brooks, W.M., Baumgartner, R.N., Sutherland, R.J., 2003. The aging hippocampus: cognitive, biochemical and structural findings. Cereb. Cortex 13, 1344–1351.
Dutt, A., McDonald, C., Dempster, E., Prata, D., Shaikh, M., Williams, I., Schulze, K., Marshall, N., Walshe, M., Allin, M., Collier, D., Murray, R., Bramon, E., 2009. The effect of COMT, BDNF, 5-HTT, NRG1 and DTNBP1 genes on hippocampal and lateral ventricular volume in psychosis. Psychol. Med. 39, 1783–1797.
Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
Ehrlich, S., Morrow, E.M., Roffman, J.L., Wallace, S.R., Naylor, M., Bockholt, H.J., Lundquist, A., Yendiki, A., Ho, B.-C., White, T., Manoach, D.S., Clark, V.P., Calhoun, V.D., Gollub, R.L., Holt, D.J., 2010. The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. Neuroimage 53, 992–1000.
Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M., Pence, B.D., Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.F., 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J. Neurosci. 30, 5368–5375.
Frielingsdorf, H., Bath, K.G., Soliman, F., Difede, J., Casey, B.J., Lee, F.S., 2010. Variant brain-derived neurotrophic factor Val66Met endophenotypes: implications for posttraumatic stress disorder. Ann. N. Y. Acad. Sci. 1208, 150–157.
Frodl, T., Schüle, C., Schmitt, G., Born, C., Baghai, T., Zill, P., Bottlender, R., Rupprecht, R., Bondy, B., Reiser, M., Möller, H.-J., Meisenzahl, E.M., 2007. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. Arch. Gen. Psychiatry 64, 410–416.
Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, O., Stieglitz, R.-D., Vita, A., McGuire, P., Borgwardt, S., 2012. Cognitive functioning in prodromal psychosis: a meta-analysis. Arch. Gen. Psychiatry 69, 562–571.
Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37, 1680–1691.
Gatt, J.M., Nemeroff, C.B., Dobson-Stone, C., Paul, R.H., Bryant, R.A., Schofield, P.R., Gordon, E., Kemp, A.H., Williams, L.M., 2009. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol. Psychiatry 14, 681–695.
Gerritsen, L., Tendolkar, I., Franke, B., Vasquez, A.A., Kooijman, S., Buitelaar, J., Fernández, G., Rijpkema, M., 2012. BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. Mol. Psychiatry 17, 597–603.
Geuze, E., Vermetten, E., Bremner, J.D., 2005. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Mol. Psychiatry 10, 160–184.
Goldman, A.L., Pezawas, L., Mattay, V.S., Fischl, B., Verchinski, B.A., Zoltick, B., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Heritability of brain morphology related to schizophrenia: a large-scale automated magnetic resonance imaging segmentation study. Biol. Psychiatry 63, 475–483.
Goldstein, J.M., Seidman, L.J., Horton, N.J., Makris, N., Kennedy, D.N., Caviness Jr., V.S., Faraone, S.V., Tsuang, M.T., 2001. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb. Cortex 11, 490–497.
Gonul, A.S., Kitis, O., Eker, M.C., Eker, O.D., Ozan, E., Coburn, K., 2011. Association of the brain-derived neurotrophic factor Val66Met polymorphism with hippocampus volumes in drug-free depressed patients. World J. Biol. Psychiatry 12, 110–118.
Goodro, M., Sameti, M., Patenaude, B., Fein, G., 2012. Age effect on subcortical structures in healthy adults. Psychiatry Res.: Neuroimaging 203, 38–45.
Gruber, O., Hasan, A., Scherk, H., Wobrock, T., Schneider-Axmann, T., Ekawardhani, S., Schmitt, A., Backens, M., Reith, W., Meyer, J., Falkai, P., 2012. Association of the brain-derived neurotrophic factor val66met polymorphism with magnetic resonance spectroscopic markers in the human hippocampus: in vivo evidence for effects on the glutamate system. Eur. Arch. Psychiatry Clin. Neurosci. 262, 23–31.
Hajek, T., Kopecek, M., Höschl, C., 2012. Reduced hippocampal volumes in healthy carriers of brain-derived neurotrophic factor Val66Met polymorphism: meta-analysis. World J. Biol. Psychiatry 13, 178–187.
Hariri, A.R., Goldberg, T.E., Mattay, V.S., Kolachana, B.S., Callicott, J.H., Egan, M.F., Weinberger, D.R., 2003. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J. Neurosci. 23, 6690–6694.
Hashimoto, R., Moriguchi, Y., Yamashita, F., Mori, T., Nemoto, K., Okada, T., Hori, H., Noguchi, H., Kunugi, H., Ohnishi, T., 2008. Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity. Neurosci. Res. 61, 360–367.
Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558.
Honea, R., Verchinski, B.A., Pezawas, L., Kolachana, B.S., Callicott, J.H., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2009. Impact of interacting functional variants in COMT on regional gray matter volume in human brain. Neuroimage 45, 44–51.
Ioannidis, J.P.A., Patsopoulos, N.A., Evangelou, E., 2007. Heterogeneity in meta-analyses of genome-wide association investigations. PLoS ONE 2, e841.
Jessen, F., Schuhmacher, A., von Widdern, O., Guttenthaler, V., Hofels, S., Suliman, H., Scheef, L., Block, W., Urbach, H., Maier, W., Zobel, A., 2009. No association of the Val66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression. Psychiatr. Genet. 19, 99–101.
Joffe, R.T., Gatt, J.M., Kemp, A.H., Grieve, S., Dobson-Stone, C., Kuan, S.A., Schofield, P.R., Gordon, E., Williams, L.M., 2009. Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: implications for depressive illness. Hum. Brain Mapp. 30, 1246–1256.
Kambeitz, J.P., Bhattacharyya, S., Kambeitz-Ilankovic, L.M., Valli, I., Collier, D.A., McGuire, P., 2012. Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis. Neurosci. Biobehav. Rev. 36, 2165–2177.
Karg, K., Burmeister, M., Shedden, K., Sen, S., 2011. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch. Gen. Psychiatry 68, 444–454.
Karnik, M.S., Wang, L., Barch, D.M., Morris, J.C., Csernansky, J.G., 2010. BDNF polymorphism rs6265 and hippocampal structure and memory performance in healthy control subjects. Psychiatry Res. 178, 425–429.
Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I.W., Moffitt, T.E., 2006. MAOA, maltreatment, and gene–environment interaction predicting children's mental health: new evidence and a meta-analysis. Mol. Psychiatry 11, 903–913.
Knickmeyer, R.C., Wang, J., Zhu, H., Geng, X., Woolson, S., Hamer, R.M., Konneker, T., Lin, W., Styner, M., Gilmore, J.H., 2013. Common variants in psychiatric risk genes predict brain structure at birth. Cereb. Cortex, http://dx.doi.org/10.1093/cercor/bhs401, Epub ahead of print.
Koolschijn, P.C.M.P., van Haren, N.E.M., Bakker, S.C., Hoogendoorn, M.L.C., Hulshoff Pol, H.E., Kahn, R.S., 2010. Effects of brain-derived neurotrophic factor Val66Met polymorphism on hippocampal volume change in schizophrenia. Hippocampus 20, 1010–1017.
Korte, M., Carroll, P., Wolf, E., Brem, G., Thoenen, H., Bonhoeffer, T., 1995. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc. Natl. Acad. Sci. U. S. A. 92, 8856–8860.
Lipsey, M.W., Wilson, D.B., 2000. Practical Meta-Analysis. SAGE, Thousand Oaks, Calif.
Liu, J., Morgan, M., Hutchison, K., Calhoun, V.D., 2010. A study of the influence of sex on genome wide methylation. PLoS ONE 5, e10028.
Lu, B., Gottschalk, W., 2000. Modulation of hippocampal synaptic transmission and plasticity by neurotrophins. Prog. Brain Res. 128, 231–241.
Lu, B., Nagappan, G., Guan, X., Nathan, P.J., Wren, P., 2013. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat. Rev. Neurosci. 14, 401–416.
Malykhin, N.V., Bouchard, T.P., Camicioli, R., Coupland, N.J., 2008. Aging hippocampus and amygdala. Neuroreport 19, 543–547.
Mandelman, S.D., Grigorenko, E.L., 2012. BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association. Genes Brain Behav. 11, 127–136.
Milner, B., Squire, L.R., Kandel, E.R., 1998. Cognitive neuroscience and the study of memory. Neuron 20, 445–468.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int. J. Surg. 8, 336–341.
Molendijk, M.L., Bus, B.A.A., Spinhoven, P., Kaimatzoglou, A., Oude Voshaar, R.C., Penninx, B.W.J.H., van IJzendoorn, M.H., Elzinga, B.M., 2012a. A systematic review and meta-analysis on the association between BDNF val(66)met and hippocampal volume–a genuine effect or a winners curse? Am. J. Med. Genet. B: Neuropsychiatr. Genet. 159B, 731–740.
Molendijk, M.L., van Tol, M.-J., Penninx, B.W.J.H., van der Wee, N.J.A., Aleman, A., Veltman, D.J., Spinhoven, P., Elzinga, B.M., 2012b. BDNF val66met affects hippocampal volume and emotion-related hippocampal memory activity. Transl. Psychiatry 2, e74.
Montag, C., Weber, B., Fliessbach, K., Elger, C., Reuter, M., 2009. The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. Psychol. Med. 39, 1831–1839.
Morey, R.A., Petty, C.M., Xu, Y., Hayes, J.P., Wagner 2nd, H.R., Lewis, D.V., LaBar, K.S., Styner, M., McCarthy, G., 2009. A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. Neuroimage 45, 855–866.
Mueller, S.C., Aouidad, A., Gorodetsky, E., Goldman, D., Pine, D.S., Ernst, M., 2013. Gray matter volume in adolescent anxiety: an impact of the brain-derived neurotrophic factor Val(66)Met polymorphism. J. Am. Acad. Child Adolesc. Psychiatry 52, 184–195.

Munafò, M.R., Freimer, N.B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Järvelin, M.-R., Taanila, A., Flint, J., 2009. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. Am. J. Med. Genet. B: Neuropsychiatr. Genet. 150B, 271–281.

Nemoto, K., Ohnishi, T., Mori, T., Moriguchi, Y., Hashimoto, R., Asada, T., Kunugi, H., 2006. The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. Neurosci. Lett. 397, 25–29.

Ninan, I., Bath, K.G., Dagar, K., Perez-Castro, R., Plummer, M.R., Lee, F.S., Chao, M.V., 2010. The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus. J. Neurosci. 30, 8866–8870.

Pang, P.T., Teng, H.K., Zaitsev, E., Woo, N.T., Sakata, K., Zhen, S., Teng, K.K., Yung, W.-H., Hempstead, B.L., Lu, B., 2004. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306, 487–491.

Park, H., Poo, M., 2013. Neurotrophin regulation of neural circuit development and function. Nat. Rev. Neurosci. 14, 7–23.

Pastalkova, E., Serrano, P., Pinkhasova, D., Wallace, E., Fenton, A.A., Sacktor, T.C., 2006. Storage of spatial information by the maintenance mechanism of LTP. Science 313, 1141–1144.

Peper, J.S., Brouwer, R.M., Boomsma, D.I., Kahn, R.S., Hulshoff Pol, H.E., 2007. Genetic influences on human brain structure: a review of brain imaging studies in twins. Hum. Brain Mapp. 28, 464–473.

Pezawas, L., Verchinski, B.A., Mattay, V.S., Callicott, J.H., Kolachana, B.S., Straub, R.E., Egan, M.F., Meyer-Lindenberg, A., Weinberger, D.R., 2004. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J. Neurosci. 24, 10099–10102.

R Core Team, 2012. R: A Language and Environment for Statistical Computing.

Raz, N., Ghisletta, P., Rodrigue, K.M., Kennedy, K.M., Lindenberger, U., 2010. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. Neuroimage 51, 501–511.

Richter-Schmidinger, T., Alexopoulos, P., Horn, M., Maus, S., Reichel, M., Rhein, C., Lewczuk, P., Sidiropoulos, C., Kneib, T., Perneczky, R., Doerfler, A., Kornhuber, J., 2011. Influence of brain-derived neurotrophic-factor and apolipoprotein E genetic variants on hippocampal volume and memory performance in healthy young adults. J. Neural Transm. 118, 249–257.

Ruigrok, A.N.V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M.V., Tait, R.J., Suckling, J., 2013. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev..

Sanchez, M.M., Das, D., Taylor, J.L., Noda, A., Yesavage, J.A., Salehi, A., 2011. BDNF polymorphism predicts the rate of decline in skilled task performance and hippocampal volume in healthy individuals. Transl. Psychiatry 1, e51.

Schofield, P.R., Williams, L.M., Paul, R.H., Gatt, J.M., Brown, K., Luty, A., Cooper, N., Grieve, S., Dobson-Stone, C., Morris, C., Kuan, S.A., Gordon, E., 2009. Disturbances in selective information processing associated with the BDNF Val66Met polymorphism: evidence from cognition, the P300 and fronto-hippocampal systems. Biol. Psychol. 80, 176–188.

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2009. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?—A systematic review. Curr. Pharm. Des. 15, 2535–2549.

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2010. Neuroimaging predictors of transition to psychosis—a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 34, 1207–1222.

Smith, G.N., Thornton, A.E., Lang, D.J., Macewan, G.W., Ehmann, T.S., Kopala, L.C., Tee, K., Shiau, G., Voineskos, A.N., Kennedy, J.L., Honer, W.G., 2012. Hippocampal volume and the brain-derived neurotrophic factor Val66Met polymorphism in first episode psychosis. Schizophr. Res. 134, 253–259.

Soliman, F., Glatt, C.E., Bath, K.G., Levita, L., Jones, R.M., Pattwell, S.S., Jing, D., Tottenham, N., Amso, D., Somerville, L.H., Voss, H.U., Glover, G., Ballon, D.J., Liston, C., Teslovich, T., Van Kempen, T., Lee, F.S., Casey, B.J., 2010. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 327, 863–866.

Squire, L.R., Wixted, J.T., 2011. The cognitive neuroscience of human memory since H.M. Annu. Rev. Neurosci. 34, 259–288.

Stein, J.L., Medland, S.E., Vasquez, A.A., Hibar, D.P., Senstad, R.E., Winkler, A.M., Toro, R., Appel, K., Bartecek, R., Bergmann, Ø., Bernard, M., Brown, A.A., Cannon, D.M., Chakravarty, M.M., Christoforou, A., Domin, M., Grimm, O., Hollinshead, M., Holmes, A.J., Homuth, G., Hottenga, J.-J., Langan, C., Lopez, L.M., Hansell, N.K., Hwang, K.S., Kim, S., Laje, G., Lee, P.H., Liu, X., Loth, E., Lourdusamy, A., Mattingsdal, M., Mohnke, S., Maniega, S.M., Nho, K., Nugent, A.C., O'Brien, C., Papmeyer, M., Pütz, B., Ramasamy, A., Rasmussen, J., Rijpkema, M., Risacher, S.L., Roddey, J.C., Rose, E.J., Ryten, M., Shen, L., Sprooten, E., Strengman, E., Teumer, A., Trabzuni, D., Turner, J., van Eijk, K., van Erp, T.G.M., van Tol, M.-J., Wittfeld, K., Wolf, C., Woudstra, S., Aleman, A., Alhusaini, S., Almasy, L., Binder, E.B., Brohawn, D.G., Cantor, R.M., Carless, M.A., Corvin, A., Czisch, M., Curran, J.E., Davies, G., de Almeida, M.A.A., Delanty, N., Depondt, C., Duggirala, R., Dyer, T.D., Erk, S., Fagerness, J., Fox, P.T., Freimer, N.B., Gill, M., Göring, H.H.H., Hagler, D.J., Hoehn, D., Holsboer, F., Hoogman, M., Hosten, N., Jahanshad, N., Johnson, M.P., Kasperaviciute Jr., D., Kochunov, J.W.K., Lancaster, P., Lawrie, J.L., Liewald, S.M., Mandl, D.C., Matarin, R., Mattheisen, M., Meisenzahl, M., Melle, E., Moses, I., Mühleisen, E.K., Nauck, T.W., Nöthen, M., Olvera, M.M., Pandolfo, R.L., Pike, M., Puls, G.B., Reinvang, R., Rentería, I., Rietschel, M.E., Roffman, M., Royle, J.L., Rujescu, N.A., Savitz, D., Schnack, J., Schnell, H.G., Seiferth, K., Smith, N., Steen, C., Valdés Hernández, V.M., Van den Heuvel, M.C., van der Wee, M., Van Haren, N.J., Veltman, N.E.M., Völzke, J.A., Walker, H., Westlye, R., Whelan, L.T., Agartz, C.D., Boomsma, I., Cavalleri, D.I., Dale, G.L., Djurovic, A.M., Drevets, S., Hagoort, W.C., Hall, P., Heinz Jr., J.A., Foroud, C.R.J., Le Hellard, T.M., Macciardi, S., Montgomery, F., Poline, G.W., Porteous, J.B., Sisodiya, D.J., Starr, S.M., Sussmann, J.M., Toga, J., Veltman, A.W., Walter, D.J., Weiner, H., (adni), M.W., the, A.D.N.I., Consortium, E., Consortium, I., (sys), S.Y.S.G., Bis, J.C., Ikram, M.A., Smith, A.V., Gudnason, V., Tzourio, C., Vernooij, M.W., Launer, L.J., DeCarli, C., Seshadri, S., Consortium, C., for, H., in, A.R., (CHARGE), G.E., Consortium, the, E.N.I.G., through, M.-A., (ENIGMA), 2012. Identification of common variants associated with human hippocampal and intracranial volumes. Nat. Genet. 44, 552–561.

Stern, A.J., Savostyanova, A.A., Goldman, A., Barnett, A.S., van der Veen, J.W.C., Callicott, J.H., Mattay, V.S., Weinberger, D.R., Marenco, S., 2008. Impact of the brain-derived neurotrophic factor Val66Met polymorphism on levels of hippocampal N-acetyl-aspartate assessed by magnetic resonance spectroscopic imaging at 3 Tesla. Biol. Psychiatry 64, 856–862.

Sullivan, E.V., Pfefferbaum, A., Swan, G.E., Carmelli, D., 2001. Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. Hippocampus 11, 754–762.

Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry 60, 1187–1192.

Szeszko, P.R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., Ashtari, M., Napolitano, B., Bilder, R.M., Kane, J.M., Goldman, D., Malhotra, A.K., 2005. Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. Mol. Psychiatry 10, 631–636.

Takahashi, T., Suzuki, M., Tsunoda, M., Kawamura, Y., Takahashi, N., Tsuneki, H., Kawasaki, Y., Zhou, S.-Y., Kobayashi, S., Sasaoka, T., Seto, H., Kurachi, M., Ozaki, N., 2008. Association between the brain-derived neurotrophic factor Val66Met polymorphism and brain morphology in a Japanese sample of schizophrenia and healthy comparisons. Neurosci. Lett. 435, 34–39.

Taylor, W.D., Züchner, S., Payne, M.E., Messer, D.F., Doty, T.J., MacFall, J.R., Beyer, J.L., Krishnan, K.R.R., 2007. The COMT Val158Met polymorphism and temporal lobe morphometry in healthy adults. Psychiatry Res. 155, 173–177.

Toro, R., Chupin, M., Garnero, L., Leonard, G., Perron, M., Pike, B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2009. Brain volumes and Val66Met polymorphism of the BDNF gene: local or global effects? Brain Struct. Funct. 213, 501–509.

Von Bohlen und Halbach, O., 2010. Involvement of BDNF in age-dependent alterations in the hippocampus. Front. Aging Neurosci., 2.

Walhovd, K.B., Westlye, L.T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D.H., Greve, D.N., Fischl, B., Dale, A.M., Fjell, A.M., 2011. Consistent neuroanatomical age-related volume differences across multiple samples. Neurobiol. Aging 32, 916–932.

Walter, A., Studerus, E., Smieskova, R., Kuster, P., Aston, J., Lang, U.E., Radue, E.-W., Riecher-Rössler, A., Borgwardt, S., 2012. Hippocampal volume in subjects at high risk of psychosis: a longitudinal MRI study. Schizophr. Res. 142, 217–222.

Wei, Q., Kang, Z., Diao, F., Shan, B., Li, L., Zheng, L., Guo, X., Liu, C., Zhang, J., Zhao, J., 2012. Association of the ZNF804A gene polymorphism rs1344706 with white matter density changes in Chinese schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 36, 122–127.

Westfall, P.H., 1993. Resampling-Based Multiple Testing: Examples and Methods for *P*-Value Adjustment. John Wiley & Sons, New York.

Wolfgang Viechtbauer, 2010. Conducting meta-analyses in {R} with the {metafor} package. J. Stat. Softw. 36, 1–48.

Yang, X., Liu, P., Sun, J., Wang, G., Zeng, F., Yuan, K., Liu, J., Dong, M., von Deneen, K.M., Qin, W., Tian, J., 2012. Impact of brain-derived neurotrophic factor Val66Met polymorphism on cortical thickness and voxel-based morphometry in healthy Chinese young adults. PLoS ONE 7, e37777.

5. DISCUSSION

In summary in this thesis we investigated sex dependency and genetic modulation (specifically by three genes: *NTRK2*, *PRKCA* and *BDNF*) of emotional processing and memory by combining several approaches and methods from various research fields (neuroimaging, genetics, epigenetics and psychoneuroendocrinology). Specifically in Spalek et al. (in preparation (a)) we analysed sex-dependent differences in emotional processing and memory performance, as well as the relation between these differences. Further, we focused in Ackermann et al. (2012) on the role of endogenous testosterone levels in emotional processing and its neuronal correlates as well as subsequent memory performance in order to better understand its potential sex-specific role in these processes. At the genetic level, we first examined in Spalek et al. (in preparation (b)) if *NTRK2* is relevant also in the context of emotion processing in healthy subjects given the extensive evidence in literature of *NTRK2* involvement in psychiatric diseases (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta et al., 2013; Hauger et al., 2009; Hill, 2012; Kohli et al., 2010; Mahan & Ressler, 2012; Marsden, 2013), which posses as main characteristic emotion dysregulation (Cole, Michel, & Teti, 1994; Kring & Sloan, 2009). Additionally, we investigated to what extend it is related to differences in brain structure as well as in methylation levels. Next, given the essential role of protein kinases in basic molecular processes of memory, in de Quervain et al. (2012) we looked for associations between genes encoding for protein kinases and memory performance. Finally, in Harrisberger et al. (2014) we investigated, if a variant in the *BDNF* gene is related to hippocampal volume, since the hippocampus is playing an essential role in memory (Squire & Wixted, 2011).

Due to the broadness of these topics (sex dependency and genetic modulation) in the following the publications will be discussed within their topical categories by first summarizing the results, then highlighting the conclusions, third pointing out some limitations, and last outline possible clinical implications.

Concerning the role of sex in emotional processing and memory, in our publication "Gender-dependent dissociation between emotional appraisal and memory: a large–scale behavioural and fMRI study" (Spalek et al., in preparation (a)) we analysed the behavioural data of four different samples, comprising 3'398 subjects. We were able to show that the women's stronger appraisal of emotional material, especially for the negative valence, is accompanied by a stronger activation of motor-relevant brain regions as well as the posterior cingulate. However, this stronger reactivity in the encoding phase was not linked to sex-dependent differences in memory performance, although we could show that across sexes

emotional stimuli were remembered better than neutral stimuli. By comparing the memory data of two different tasks, a free-recall task and a recognition task, we were able to show that sex differences regarding memory performance were retrieval setting-dependent. Specifically, women outperformed men only in the free recall task, but not in the recognition task, suggesting that there was no sex-dependent difference in memory storage. In the publication "Testosterone levels in healthy men are related to amygdala reactivity and memory performance" (Ackermann et al., 2012) we identified increased emotional arousal ratings as well as higher amygdala reactivity to neutral pictures with increasing testosterone levels in men, but not in women. Further, increased endogenous testosterone levels in men, but not in women, were related to better memory recall of these neutral pictures.

Taken together, the findings from these two publications provide evidence for sex differences on the level of emotional processing with related neuronal activation differences as well as in memory performance in specific task settings. Furthermore, amygdala activation during processing and additionally memory performance of specifically neutral stimuli are modulated by endogenous testosterone levels, but only in men. This may point to a male-specific role of testosterone in enhancing memory by increasing the biological salience of incoming information. These findings add valuable knowledge about the presence of sex differences in these cognitive domains and point out the importance of controlling for the influence of sex in analyses.

Some limitations of the presented studies should be considered. Based on the results of the publication "Gender-dependent dissociation between emotional appraisal and memory: a large–scale behavioural and fMRI study" (Spalek et al., in preparation (a)) we suggested that there was no sex-dependent difference in memory storage. The validity of this assessment could theoretically be further verified, if imaging during the free recall task would have been performed. However this is difficult to implement in terms of feasibility. Another aspect concerns the fact that verbal skills and motivational aspects could have influenced the better memory performance of females in the free recall task. This is further supported by the disappearance of female's advantage in the recognition task, since both verbal skills and motivational aspects are likely to play a less important role there. Concerning our publication "Testosterone levels in healthy men are related to amygdala reactivity and memory performance" (Ackermann et al., 2012) the relatively small sample size especially of men (n = 96) has to be mentioned as a limitation. Additionally, it would have been interesting to investigate the possibility of amygdala activation mediating the effect of testosterone levels on either arousal ratings and memory performance. Two more limitations concern the

testosterone measurement. First, due to the pulsatile release of testosterone it would have been more reliable to measure testosterone levels based on several samples, not just one. Second, we cannot rule out that the absence of the effect in women might be due to the method used for testosterone measurement (cotton salivettes; Wirth, Stanton, Gaffey, & Liening, 2012).

Possible clinical implications of these findings stem mainly from the higher appraisal of emotional stimuli, especially negative stimuli, by women. This stronger appraisal might be related to their increased vulnerability to psychiatric diseases (Culbertson, 1997; Earls, 1987; Holden, 2005; Weinstock, 1999), which have emotional dysregulation as a common component (Cole, Michel, & Teti, 1994; Kring & Sloan, 2009). Additionally, the differences in brain activation during the emotion processing task in motor-relevant regions as well as posterior cingulate might even point to an increased physical reactivity of women to negative stimuli, which is also supported by other studies (Bradley et al., 2001; Gard & Kring, 2007; Kring & Gordon, 1998; Lithari et al., 2010).

In the context of genetic modulation, we showed that emotion processing in healthy young subjects is associated with a *NTRK2* genotype variant. Specifically, in the publication "Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects" (Spalek et al., in preparation (a)) we identified an association between a genetic variant of *NTRK2* (rs2579372) and emotional arousal ratings given during assessment of positive IAPS pictures by two separate samples of healthy young subjects (n_1 = 1'171, n_2 = 707). Furthermore, we observed genotype-dependent differences in methylation levels. In a genotype-independent analysis of DTI data from 342 subjects (subpopulation of n_2), we found a negative correlation between mean positive arousal ratings and MD values in tracts belonging to the limbic circuits or forming connections from other brain regions to these circuits. We also observed genotype-dependent differences in MD values. Interestingly, the regions showing genotype-dependent differences in MD values largely overlapped with the regions showing significant correlations between MD values and emotional arousal. In the second publication "PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors" (de Quervain et al., 2012) we show that a genetic variant of the *PRKCA* gene (rs4790904) is associated with memory performance in two independent samples (n_1 = 723, n_2 = 394) of healthy young subjects. Additionally, in the bigger sample long-term memory performance data (24 hours delayed free recall of same picture data) were available and showed as well genotype-dependent differences in memory performance. In the fMRI data, available from the smaller sample, genotype-dependent brain activation differences in the lateral and medial PFC

were observed during the successful encoding of negative IAPS pictures. This genetic variant was also related to PTSD-related symptoms (intrusions and avoidance) as well as risk for PTSD diagnose in a sample of heavily traumatized genocide survivors ($n_3 = 347$). Finally, the findings from the publication "The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data" (Harrisberger et al., 2014) do not support the association of the SNP rs6265 on the *BDNF* gene and hippocampal volumes based on the original data of 643 healthy young subjects. The meta-analysis revealed a weak effect, which was mainly driven by studies with small sample sizes applying manual segmentation of hippocampi. Additionally, effect sizes decreased with increasing sample size over the years, but only for manual tracing samples. Our results are based on a large sample size and confirm the findings of previous publications. Moreover our findings demonstrate an effect of measuring techniques, publication year and sample size.

Highlighting the main conclusions, in a first step we provide evidence for a genetic modulation of emotional processing by a genetic variant in *NTRK2* gene in healthy young subjects, while so far *NTRK2* was found to be associated only with psychiatric diseases (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta et al., 2013; Hauger et al., 2009; Hill, 2012; Kohli et al., 2010; Mahan & Ressler, 2012; Marsden, 2013). By genotype-dependent differences in methylation levels we further point to a functional consequence of the *NTRK2* variant with regard to gene regulation. In a next step, our findings about *PRKCA* illustrate a role of protein kinase C alpha (PKCα) in memory performance on one hand in healthy young subjects and on the other hand with traumatic memory and risk for PTSD in genocide survivors. Ultimately, our findings do not support the association of a genetic variant in the *BDNF* gene and hippocampal volumes. Even though, the absence of difference on the anatomical level does not rule out that *BDNF* modulates other processes in the hippocampus. However, results from studies examining *BDNF*-dependent differences in hippocampal activation during memory paradigms (Cerasa et al., 2010; Dennis et al., 2011; Egan et al., 2003; Hariri et al., 2003; Hashimoto et al., 2008; Kambeitz et al., 2012; Molendijk et al., 2012) or directly investigating *BDNF*-dependent differences in memory performance (Kambeitz et al., 2012; Mandelman & Grigorenko, 2012) are inconsistent.

Several limitations have to be taken into account in these three publications. One could argue that a limitation of the publication "Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects" (Spalek et al., in preparation (b)) is the absence of an association of *NTRK2* and

mean negative arousal ratings. However this might just be due to the specificity of the effect on positive stimuli, supported by the results from the structural data. A further limitation might be that there were no genotype-dependent differences in exactly the voxels showing a significant association between MD values and mean positive arousal ratings. Even though tracts with a significant correlation between mean positive arousal ratings and MD values were to a large extend the same ones as tracts showing genotype-dependent differences. In the publication "PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors" (de Quervain et al., 2012) a possible limitation is that in the hypothesis-testing sample genotype-dependent differences in short-term memory performance were present in all three pictures categories (negative, positive and neutral), whereas in the long-delay performance in the same sample significant differences appeared only in the negative and neutral picture category as well as in the replication sample only memory performance of negative and positive reached significance, which might be due to less power given by the smaller sample size. But generally, these findings indicate that the association of the *PRKCA* genetic variant is consistent for negative pictures as well as the overall memory performance (all picture categories). Concerning the fMRI results, it might be counterintuitive that there were no significant genotype-dependent differences in temporal lobe regions (e.g. amygdala and hippocampus). This might be due to the fact that fMRI data were collected at the encoding stage, whereas genotype-dependent differences in temporal lobe regions might occur at a later stage in memory processes. Additionally, no activation differences were observed for subsequent memory of positive pictures, where behavioural differences were as well present. This points to a specificity of genotype-dependent differences on a functional level only for negative stimuli. Finally, regarding the analyses about the association of *BDNF* and hippocampal volumes in the publication "The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data" (Harrisberger et al., 2014) three limitations have to be taken into account. First, we did not address laterality differences or differences in specific hippocampal sub-regions due to the fact that many studies included in the meta-analysis reported only total hippocampal volumes. Second, we focused only on the *BDNF* SNP rs6265 and did not consider other SNPs, gene-gene interactions or gene-environment interactions. Last, we did not observe any sex- or age-dependent differences in hippocampal volumes as found by other studies (sex differences: Cahill, 2006; Goldstein et al., 2001; Liu, Morgan, Hutchison, & Calhoun, 2010; Ruigrok et al., 2014; age differences: Driscoll et al., 2003; Malykhin, Bouchard, Camicioli, & Coupland, 2008; Raz, Ghisletta, Rodrigue,

Kennedy, & Lindenberger, 2010). This might be due to the applied correction for ICV and a limited age-range in our data.

There might be some clinical implications arising from the findings in the publication "Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects" (Spalek et al., in preparation (b)). Our results of an association between *NTRK2* and mean positive arousal ratings in healthy subjects in connection with the knowledge about altered rating of emotionally arousing IAPS pictures in patients with psychiatric disorders (Aguilar de Arcos et al., 2008; Aguilar de Arcos, Verdejo-García, Peralta-Ramírez, Sánchez-Barrera, & Pérez-García, 2005; Aminoff, Jensen, Lagerberg, Andreassen, & Melle, 2011; Jayaro et al., 2011; Lee et al., 2007; Strauss & Herbener, 2011), and several genetic associations between *NTRK2* and psychopathology (Alonso et al., 2008; Boulle et al., 2012; Deo et al., 2013; Ernst et al., 2011; Gupta et al., 2013; Hauger et al., 2009; Hill, 2012; Kohli et al., 2010; Li et al., 2013; Lin et al., 2009; Mahan & Ressler, 2012; Marsden, 2013; Ribases et al., 2005), point to a role of *NTRK2* in emotion processing in healthy subjects and patients with psychiatric disorders. Tracts identified in our DTI analysis were located in regions central for emotion processing and are reported by several studies to show alterations in patients with different psychiatric disorders like obsessive compulsive disorder, bipolar disorder, autism spectrum disorder, antisocial personality disorder and schizophrenia (Fontenelle et al., 2011; Lu, Zhou, Keedy, Reilly, & Sweeney, 2011; Sundram et al., 2012; Travers et al., 2012; Zanetti et al., 2009). Interestingly, several studies provide evidence for a contribution of *NTRK2* gene variants to the genetic susceptibility to various psychiatric disorders (Alonso et al., 2008; Li et al., 2013; Lin et al., 2009; Ribases et al., 2005). Having asserted that, it remains to be thoroughly investigated if *NTRK2* might be a predictive biomarker of vulnerability to psychiatric disorders. Last the publication "PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors" (de Quervain et al., 2012) provides clinical implications by suggesting a genetic link between the predisposition to build strong memories and the risk for PTSD. Additionally, the results indicate differential genetic risks for different PTSD symptoms, which might provide useful information for the understanding and possible treatment of PTSD.

Overall, both genetic factors and differences due to sex play an essential role within emotion processing as well as memory, and their understanding might improve the knowledge about psychopathology and treatment possibilities. As illustrated by this thesis, the

combination of methods from different fields seems to be a promising way for uncovering and combining puzzle pieces of complex cognitive processes undermining our behaviour.

6. REFERENCES

Abdelgadir, S. E., Roselli, C. E., Choate, J. V., & Resko, J. A. (1999). Androgen receptor messenger ribonucleic acid in brains and pituitaries of male rhesus monkeys: studies on distribution, hormonal control, and relationship to luteinizing hormone secretion. *Biology of reproduction*, *60*(5), 1251-6.

Ackermann, S., Hartmann, F., Papassotiropoulos, A., de Quervain, D. J. F., & Rasch, B. (2013). Associations between basal cortisol levels and memory retrieval in healthy young individuals. *Journal of cognitive neuroscience*, *25*(11), 1896-907.

Ackermann, S., Spalek, K., Rasch, B., Gschwind, L., Coynel, D., Fastenrath, M., Papassotiropoulos, A., et al. (2012). Testosterone levels in healthy men are related to amygdala reactivity and memory performance. *Psychoneuroendocrinology*, *37*(9), 1417-1424.

Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., López-Jiménez, A., et al. (2008). Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. *Psychopharmacology*, *198*(2), 159-66.

Aguilar de Arcos, F., Verdejo-García, A., Peralta-Ramírez, M. I., Sánchez-Barrera, M., & Pérez-García, M. (2005). Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug and alcohol dependence*, *78*(2), 159-67.

Alger, J. R. (2012). The diffusion tensor imaging toolbox. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *32*(22), 7418-28.

Alonso, P., Gratacòs, M., Menchón, J. M., Saiz-Ruiz, J., Segalàs, C., Baca-García, E., Labad, J., et al. (2008). Extensive genotyping of the BDNF and NTRK2 genes define protective haplotypes against obsessive-compulsive disorder. *Biological psychiatry*, *63*(6), 619-28.

Aminoff, S. R., Jensen, J., Lagerberg, T. V., Andreassen, O. A., & Melle, I. (2011). Decreased self-reported arousal in schizophrenia during aversive picture viewing compared to bipolar disorder and healthy controls. *Psychiatry research*, *185*(3), 309-14.

Andreano, J. M., & Cahill, L. (2009). Sex influences on the neurobiology of learning and memory. *Learning & memory*, *16*(4), 248-66.

Bailey, C. H., & Kandel, E. R. (2008). Synaptic remodeling, synaptic growth and the storage of long-term memory in Aplysia. *Progress in brain research*, *169*, 179-98.

Baj, G., Carlino, D., Gardossi, L., & Tongiorgi, E. (2013). Toward a unified biological hypothesis for the BDNF Val66Met-associated memory deficits in humans: a model of impaired dendritic mRNA trafficking. *Frontiers in neuroscience*, *7*, 188.

Barco, A., Bailey, C. H., & Kandel, E. R. (2006). Common molecular mechanisms in explicit and implicit memory. *Journal of neurochemistry*, *97*(6), 1520-33.

Barrett-Connor, E., Goodman-Gruen, D., & Patay, B. (1999). Endogenous sex hormones and cognitive function in older men. *The Journal of clinical endocrinology and metabolism*, *84*(10), 3681-5.

Basser, P. J. (1995). Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in biomedicine*, *8*(7-8), 333-44.

Bear, M., Connors, B., & Paradiso, M. (2009). *Neurowissenschaften. Ein grundlegendes Lehrbuch für Biologie, Medizin und Psychologie*. Heidelberg: Spektrum Akademischer Verlag.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in biomedicine*, *15*(7-8), 435-55.

Bergado, J. A., Lucas, M., & Richter-Levin, G. (2011). Emotional tagging--a simple hypothesis in a complex reality. *Progress in neurobiology*, *94*(1), 64-76.

Bevilacqua, L., & Goldman, D. (2011). Genetics of emotion. *Trends in cognitive sciences*, *15*(9), 401-8.

Beyenburg, S., Watzka, M., Clusmann, H., Blümcke, I., Bidlingmaier, F., Elger, C. E., & Stoffel-Wagner, B. (2000). Androgen receptor mRNA expression in the human hippocampus. *Neuroscience letters*, *294*(1), 25-8.

Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth factors*, *22*(3), 123-31.

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31-9.

Bliss, T. V. P., & Cooke, S. F. (2011). Long-term potentiation and long-term depression: a clinical perspective. *Clinics*, *66 Suppl 1*, 3-17.

Bliss, T. V. P., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of physiology*, *232*(2), 331-56.

Bliss, T. V. P., & Gardner-Medwin, A. R. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. *The Journal of physiology*, *232*(2), 357-74.

Bloise, S. M., & Johnson, M. K. (2007). Memory for emotional and neutral information: gender and individual differences in emotional sensitivity. *Memory*, *15*(2), 192-204.

Boulle, F., Kenis, G., Cazorla, M., Hamon, M., Steinbusch, H. W. M., Lanfumey, L., & Hove, D. L. A. V. D. (2012). TrkB inhibition as a therapeutic target for CNS-related disorders. *Progress in Neurobiology*, *98*, 197-206.

Bradley, M. M., Codispoti, M., Sabatinelli, D., & Lang, P. J. (2001). Emotion and motivation II: sex differences in picture processing. *Emotion*, *1*(3), 300-19.

Britton, J. C., Taylor, S. F., Sudheimer, K. D., & Liberzon, I. (2006). Facial expressions and complex IAPS pictures: common and differential networks. *NeuroImage*, *31*(2), 906-19.

Buckner, R. L., & Koutstaal, W. (1998). Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 891-8.

Cahill, L. (2003). Sex-related influences on the neurobiology of emotionally influenced memory. *Annals of the New York Academy of Sciences*, *985*, 163-73.

Cahill, L. (2006). Why sex matters for neuroscience. *Nature reviews Neuroscience*, *7*(6), 477-84.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., et al. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(15), 8016-21.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *20*(19), RC99.

Cannon, W. B. (1987). The James-Lange theory of emotions: a critical examination and an alternative theory. By Walter B. Cannon, 1927. *The American journal of psychology*, *100*(3-4), 567-86.

Caviness, V. S., Lange, N. T., Makris, N., Herbert, M. R., & Kennedy, D. N. (1999). MRI-based brain volumetrics: emergence of a developmental brain science. *Brain & development*, *21*(5), 289-95.

Cerasa, A., Tongiorgi, E., Fera, F., Gioia, M. C., Valentino, P., Liguori, M., Manna, I., et al. (2010). The effects of BDNF Val66Met polymorphism on brain function in controls and patients with multiple sclerosis: an imaging genetic study. *Behavioural brain research*, *207*(2), 377-86.

Cherrier, M. M., Anawalt, B. D., Herbst, K. L., Amory, J. K., Craft, S., Matsumoto, A. M., & Bremner, W. J. (2002). Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. *The Journal of clinical endocrinology and metabolism*, *87*(7), 3090-6.

Cherrier, M. M., Matsumoto, A. M., Amory, J. K., Asthana, S., Bremner, W., Peskind, E. R., Raskind, M. A., et al. (2005). Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology*, *64*(12), 2063-8.

Clapp, W. C., Hamm, J. P., Kirk, I. J., & Teyler, T. J. (2012). Translating long-term potentiation from animals to humans: a novel method for noninvasive assessment of cortical plasticity. *Biological psychiatry*, *71*(6), 496-502.

Cole, P. M., Michel, M. K., & Teti, L. O. (1994). The development of emotion regulation and dysregulation: a clinical perspective. *Monographs of the Society for Research in Child Development*, *59*(2-3), 73-100.

Cordell, H. J. (2009). Detecting gene-gene interactions that underlie human diseases. *Nature reviews Genetics*, *10*(6), 392-404.

Culbertson, F. M. (1997). Depression and gender. An international review. *The American psychologist*, *52*(1), 25-31.

Cunha, C., Brambilla, R., & Thomas, K. L. (2010). A simple role for BDNF in learning and memory? *Frontiers in molecular neuroscience*, *3*, 1.

Dalgleish, T. (2004). The emotional brain. *Nature reviews Neuroscience*, *5*(7), 583-9.

de Frias, C. M., Nilsson, L.-G., & Herlitz, A. (2006). Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *13*(3-4), 574-87.

de Quervain, D. J.-F., Kolassa, I.-T., Ackermann, S., Aerni, A., Boesiger, P., Demougin, P., Elbert, T., et al. (2012). PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(22), 8746-51.

de Quervain, D. J.-F., Kolassa, I.-T., Ertl, V., Onyut, P. L., Neuner, F., Elbert, T., & Papassotiropoulos, A. (2007). A deletion variant of the alpha2b-adrenoceptor is related to emotional memory in Europeans and Africans. *Nature neuroscience*, *10*(9), 1137-9.

de Quervain, D. J.-F., & Papassotiropoulos, A. (2006). Identification of a genetic cluster influencing memory performance and hippocampal activity in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(11), 4270-4274.

Dennis, N. A., Cabeza, R., Need, A. C., Waters-Metenier, S., Goldstein, D. B., & LaBar, K. S. (2011). Brain-derived neurotrophic factor val66met polymorphism and hippocampal activation during episodic encoding and retrieval tasks. *Hippocampus*, *21*(9), 980-9.

Deo, A. J., Huang, Y.-Y., Hodgkinson, C. A., Xin, Y., Oquendo, M. A., Dwork, A. J., Arango, V., et al. (2013). A large-scale candidate gene analysis of mood disorders: evidence of neurotrophic tyrosine kinase receptor and opioid receptor signaling dysfunction. *Psychiatric genetics*, *23*(2), 47-55.

Derntl, B., Windischberger, C., Robinson, S., Kryspin-Exner, I., Gur, R. C., Moser, E., & Habel, U. (2009). Amygdala activity to fear and anger in healthy young males is associated with testosterone. *Psychoneuroendocrinology*, *34*(5), 687-93.

Driscoll, I., Hamilton, D. A., Petropoulos, H., Yeo, R. A., Brooks, W. M., Baumgartner, R. N., & Sutherland, R. J. (2003). The aging hippocampus: cognitive, biochemical and structural findings. *Cerebral cortex*, *13*(12), 1344-51.

Earls, F. (1987). Sex differences in psychiatric disorders: origins and developmental influences. *Psychiatric developments*, *5*(1), 1-23.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257-69.

Ekstrom, A. D., Meltzer, J., McNaughton, B. L., & Barnes, C. A. (2001). NMDA receptor antagonism blocks experience-dependent expansion of hippocampal "place fields". *Neuron*, *31*(4), 631-8.

Ernst, C., Wanner, B., Brezo, J., Vitaro, F., Tremblay, R., & Turecki, G. (2011). A deletion in tropomyosin-related kinase B and the development of human anxiety. *Biological psychiatry*, *69*(6), 604-7.

Ertman, N., Andreano, J. M., & Cahill, L. (2011). Progesterone at encoding predicts subsequent emotional memory. *Learning & memory*, *18*(12), 759-63.

Fazzari, M. J., & Greally, J. M. (2010). Introduction to epigenomics and epigenome-wide analysis. *Methods in molecular biology*, *620*, 243-65.

Fehr, F. S., & Stern, J. A. (1970). Peripheral physiological variables and emotion: the James-Lange theory revisited. *Psychological bulletin*, *74*(6), 411-24.

Fischer, A. H., Rodriguez Mosquera, P. M., Vianen, A. E. M., & Manstead, A. S. R. (2004). Gender and culture differences in emotion. *Emotion*, *4*(1), 87-94.

Fonda, S. J., Bertrand, R., O'Donnell, A., Longcope, C., & McKinlay, J. B. (2005). Age, hormones, and cognitive functioning among middle-aged and elderly men: cross-sectional evidence from the Massachusetts Male Aging Study. *The journals of gerontology. Series A, Biological sciences and medical sciences*, *60*(3), 385-90.

Fontenelle, L. F., Bramati, I. E., Moll, J., Medlowicz, M. V., de Oliveira-Souza, R., & Tovar-Moll, F. (2011). White Matter Changes in OCD Revealed by Diffusion Tensor Imaging. *CNS spectrums*, *16*(5), 101-9.

Frey, U., & Morris, R. G. (1997). Synaptic tagging and long-term potentiation. *Nature*, *385*(6616), 533-6.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., et al. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience : JPN*, *34*(6), 418-32.

Gard, M. G., & Kring, A. M. (2007). Sex differences in the time course of emotion. *Emotion*, *7*(2), 429-37.

Gasbarri, A., Tavares, M. C. H., Rodrigues, R. C., Tomaz, C., & Pompili, A. (2012). Estrogen, cognitive functions and emotion: an overview on humans, non-human primates and rodents in reproductive years. *Reviews in the neurosciences*, *23*(5-6), 587-606.

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: bridging selective attention and working memory. *Trends in cognitive sciences*, *16*(2), 129-35.

Goldstein, J. M., Seidman, L. J., Horton, N. J., Makris, N., Kennedy, D. N., Caviness, V. S., Faraone, S. V., et al. (2001). Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cerebral cortex*, *11*(6), 490-7.

Gupta, V. K., You, Y., Gupta, V. B., Klistorner, A., & Graham, S. L. (2013). TrkB Receptor Signalling: Implications in Neurodegenerative, Psychiatric and Proliferative Disorders. *International journal of molecular sciences*, *14*(5), 10122-42.

Hamann, S. (2001). Cognitive and neural mechanisms of emotional memory. *Trends in cognitive sciences*, *5*(9), 394-400.

Hamann, S. (2005). Sex differences in the responses of the human amygdala. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, *11*(4), 288-93.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature neuroscience*, *2*(3), 289-93.

Hardingham, N., Dachtler, J., & Fox, K. (2013). The role of nitric oxide in pre-synaptic plasticity and homeostasis. *Frontiers in cellular neuroscience*, *7*, 190.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *23*(17), 6690-4.

Hariri, A. R., Tessitore, A., Mattay, V. S., Fera, F., & Weinberger, D. R. (2002). The amygdala response to emotional stimuli: a comparison of faces and scenes. *NeuroImage*, *17*(1), 317-23.

Harrisberger, F., Spalek, K., Smieskova, R., Schmidt, A., Coynel, D., Milnik, A., Fastenrath, M., et al. (2014). The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: A joint meta-analysis of published and new data. *Neuroscience and biobehavioral reviews*, *42C*, 267-278.

Hashimoto, R., Moriguchi, Y., Yamashita, F., Mori, T., Nemoto, K., Okada, T., Hori, H., et al. (2008). Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity. *Neuroscience research*, *61*(4), 360-7.

Hauger, R. L., Risbrough, V., Oakley, R. H., Olivares-Reyes, J. A., & Dautzenberg, F. M. (2009). Role of CRF receptor signaling in stress vulnerability, anxiety, and depression. *Annals of the New York Academy of Sciences*, *1179*, 120-43.

Hautzel, H., Mottaghy, F. M., Schmidt, D., Zemb, M., Shah, N. J., Müller-Gärtner, H.-W., & Krause, B. J. (2002). Topographic segregation and convergence of verbal, object, shape and spatial working memory in humans. *Neuroscience letters*, *323*(2), 156-60.

Herlitz, A., Nilsson, L. G., & Bäckman, L. (1997). Gender differences in episodic memory. *Memory & cognition*, *25*(6), 801-11.

Herlitz, A., Reuterskiöld, L., Lovén, J., Thilers, P. P., & Rehnman, J. (2013). Cognitive sex differences are not magnified as a function of age, sex hormones, or puberty development during early adolescence. *Developmental neuropsychology*, *38*(3), 167-79.

Hermans, E. J., Ramsey, N. F., & van Honk, J. (2008). Exogenous testosterone enhances responsiveness to social threat in the neural circuitry of social aggression in humans. *Biological psychiatry*, *63*(3), 263-70.

Het, S., Ramlow, G., & Wolf, O. T. (2005). A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology*, *30*(8), 771-84.

Hill, R. A. (2012). Interaction of sex steroid hormones and brain-derived neurotrophic factor-tyrosine kinase B signalling: relevance to schizophrenia and depression. *Journal of neuroendocrinology*, *24*(12), 1553-61.

Hogervorst, E., Matthews, F. E., & Brayne, C. (2010). Are optimal levels of testosterone associated with better cognitive function in healthy older women and men? *Biochimica et biophysica acta*, *1800*(10), 1145-52.

Holden, C. (2005). Sex and the suffering brain. *Science*, *308*(5728), 1574-77.

Holmans, P. (2010). Statistical methods for pathway analysis of genome-wide data for association with complex genetic traits. *Advances in genetics*, *72*, 141-79.

Honk, J., & Schutter, D. J. L. G. (2007). Testosterone reduces conscious detection of signals serving social correction: implications for antisocial behavior. *Psychological science*, *18*(8), 663-7.

Huganir, R. L., & Nicoll, R. A. (2013). AMPARs and synaptic plasticity: the last 25 years. *Neuron*, *80*(3), 704-17.

Jayaro, C., De La Vega, I., Bayon-Palomino, C., Díaz-Marsá, M., Montes, A., Tajima, K., López-Ibor, J. J., et al. (2011). Depressive-type emotional response pattern in impulsive-aggressive patients with borderline personality disorder. *Journal of affective disorders*, *135*(1-3), 37-42.

Jia, P., & Zhao, Z. (2014). Network.assisted analysis to prioritize GWAS results: principles, methods and perspectives. *Human genetics*, *133*(2), 125-38.

Johansen-Berg, H., & Behrens, T. E. J. (2009). *Diffusion MRI. From Quantitative Measurement to In vivo Neuroanatomy.* Elsevier Inc.

Kambeitz, J. P., Bhattacharyya, S., Kambeitz-Ilankovic, L. M., Valli, I., Collier, D. A., & McGuire, P. (2012). Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis. *Neuroscience and biobehavioral reviews*, *36*(9), 2165-77.

Kandel, E. R. (2001). The molecular biology of memory storage: a dialogue between genes and synapses. *Science*, *294*(5544), 1030-8.

Kandel, E. R. (2012). The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Molecular brain*, *5*, 14.

Kohli, M., Salyakina, D., Pfennig, A., Lucae, S., Horstmann, S., Menke, A., Kloiber, S., et al. (2010). Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. *Archives of general psychiatry*, *67*(4), 348-59.

Kramer, J. H., Delis, D. C., Kaplan, E., O'Donnell, L., & Prifitera, A. (1997). Developmental sex differences in verbal learning. *Neuropsychology*, *11*(4), 577-84.

Kret, M. E., & Gelder, B. (2012). A review on sex differences in processing emotional signals. *Neuropsychologia*, *50*(7), 1211-21.

Kring, A. M., & Gordon, A. H. (1998). Sex differences in emotion: expression, experience, and physiology. *Journal of personality and social psychology*, *74*(3), 686-703.

Kring, A. M., & Sloan, D. M. (2009). *Emotion Regulation and Psychopathology: A Transdiagnostic Approach to Etiology and Treatment* (p. 461). New York: The Guilford Press.

Kritzer, M. (2004). The distribution of immunoreactivity for intracellular androgen receptors in the cerebral cortex of hormonally intact adult male and female rats: localization in pyramidal neurons making corticocortical connections. *Cerebral cortex*, *14*(3), 268-80.

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature reviews Neuroscience*, *7*(1), 54-64.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1998). Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. *Biological psychiatry*, *44*(12), 1248-63.

Lang, P. J., Öhmann, A., & Vaitl, D. (1988). *The International Affective Picture System (slides)*. Gainesville, FL.

LeDoux, J. (1998). Fear and the brain: where have we been, and where are we going? *Biological psychiatry*, *44*(12), 1229-38.

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and molecular neurobiology*, *23*(4-5), 727-38.

Lee, B.-T., Cho, S. W., Khang, H. S., Lee, B.-C., Choi, I.-G., Lyoo, I. K., & Ham, B.-J. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in neuro-psychopharmacology & biological psychiatry*, *31*(7), 1487-92.

Lewis, M., Haviland-Jones, J. M., & Feldman Barrett, L. (2008). *Handbook of emotions* (third edition). New York: The Guilford Press.

Li, Z., Zhang, Y., Wang, Z., Chen, J., Fan, J., Guan, Y., Zhang, C., et al. (2013). The role of BDNF, NTRK2 gene and their interaction in development of treatment-resistant depression: data from multicenter, prospective, longitudinal clinic practice. *Journal of psychiatric research*, *47*(1), 8-14.

Lin, E., Hong, C.-J., Hwang, J.-P., Liou, Y.-J., Yang, C.-H., Cheng, D., & Tsai, S.-J. (2009). Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. *Rejuvenation research*, *12*(6), 387-93.

Lisman, J., Schulman, H., & Cline, H. (2002). The molecular basis of CaMKII function in synaptic and behavioural memory. *Nature reviews Neuroscience*, *3*(3), 175-90.

Lithari, C., Frantzidis, C. A., Papadelis, C., Vivas, A. B., Klados, M. A., Kourtidou-Papadeli, C., Pappas, C., et al. (2010). Are females more responsive to emotional stimuli? A neurophysiological study across arousal and valence dimensions. *Brain topography*, *23*(1), 27-40.

Liu, J., Morgan, M., Hutchison, K., & Calhoun, V. D. (2010). A study of the influence of sex on genome wide methylation. *PloS one*, *5*(4), e10028.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869-78.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150-7.

Lu, L. H., Zhou, X. J., Keedy, S. K., Reilly, J. L., & Sweeney, J. A. (2011). White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar disorders*, *13*(7-8), 604-13.

Lu, Y., Christian, K., & Lu, B. (2008). BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of learning and memory*, *89*(3), 312-23.

Lövheim, H. (2012). A new three-dimensional model for emotions and monoamine neurotransmitters. *Medical hypotheses*, *78*(2), 341-8.

MacLean, P. D. (1955). The limbic system ("visceral brain") and emotional behavior. *A.M.A. archives of neurology and psychiatry*, *73*(2), 130-4.

Mahan, A. L., & Ressler, K. J. (2012). Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends in neurosciences*, *35*(1), 24-35.

Malenka, R. C., & Nicoll, R. A. (1999). Long-term potentiation--a decade of progress? *Science*, *285*(5435), 1870-4.

Malleret, G., Haditsch, U., Genoux, D., Jones, M. W., Bliss, T. V., Vanhoose, A. M., Weitlauf, C., et al. (2001). Inducible and reversible enhancement of learning, memory, and long-term potentiation by genetic inhibition of calcineurin. *Cell*, *104*(5), 675-86.

Malykhin, N. V., Bouchard, T. P., Camicioli, R., & Coupland, N. J. (2008). Aging hippocampus and amygdala. *Neuroreport*, *19*(5), 543-7.

Mandelman, S. D., & Grigorenko, E. L. (2012). BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association. *Genes, brain, and behavior*, *11*(2), 127-36.

Marsden, W. N. (2013). Synaptic plasticity in depression: molecular, cellular and functional correlates. *Progress in neuro-psychopharmacology & biological psychiatry*, *43*, 168-84.

Martin, K. C., & Kosik, K. S. (2002). Synaptic tagging -- who's it? *Nature reviews Neuroscience*, *3*(10), 813-20.

Mathieson, K., & Banerjee, R. (2011). Peer play, emotion understanding, and socio-moral explanation: the role of gender. *The British journal of developmental psychology*, *29*(Pt 2), 188-96.

Mayford, M., Siegelbaum, S. A., & Kandel, E. R. (2012). Synapses and memory storage. *Cold Spring Harbor perspectives in biology*, *4*(6).

McGaugh, J. L. (2000). Memory--a century of consolidation. *Science*, *287*(5451), 248-51.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: a systems perspective. *Trends in neurosciences*, *25*(9), 456.

McGaugh, J. L. (2003). *Memory and Emotion: The Making of Lasting Memories* (p. 162). London: Weidenfeld & Nicolson.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual review of neuroscience*, *27*, 1-28.

McGaugh, J. L., & Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Current opinion in neurobiology*, *12*(2), 205-10.

McGeer, P. L., & McGeer, E. G. (1980). Chemistry of mood and emotion. *Annual review of psychology*, *31*, 273-307.

McReynolds, J. R., & McIntyre, C. K. (2012). Emotional modulation of the synapse. *Reviews in the neurosciences*, *23*(5-6), 449-61.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature reviews Neuroscience*, *12*(9), 524-38.

Milnik, A., Vukojevic, V., Demougin, P., Egli, T., Freytag, V., Heck, A., Peter, F., et al. (in preparation). Array-based methylation data in the context of quantitative trait analyses.

Moffat, S. D., Zonderman, A. B., Metter, E. J., Blackman, M. R., Harman, S. M., & Resnick, S. M. (2002). Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *The Journal of clinical endocrinology and metabolism*, *87*(11), 5001-7.

Molendijk, M. L., van Tol, M.-J., Penninx, B. W. J. H., van der Wee, N. J. A., Aleman, A., Veltman, D. J., Spinhoven, P., et al. (2012). BDNF val66met affects hippocampal volume and emotion-related hippocampal memory activity. *Translational psychiatry*, *2*, e74.

Neale, B. M., Ferreira, M. A., Medland, S. E., & Posthuma, D. (2008). *Statistical Genetics. Gene Mapping Through Linkage and Association.* New York: Taylor & Francis Group.

Papassotiropoulos, A., & de Quervain, D. J.-F. (2011). Genetics of human episodic memory: dealing with complexity. *Trends in cognitive sciences*, *15*(9), 381-7.

Papez, J. W. (1995). A proposed mechanism of emotion. 1937. *The Journal of neuropsychiatry and clinical neurosciences*, *7*(1), 103-12.

Perry, P. J., Lund, B. C., Arndt, S., Holman, T., Bever-Stille, K. A., Paulsen, J., & Demers, L. M. (2001). Bioavailable testosterone as a correlate of cognition, psychological status, quality of life, and sexual function in aging males: implications for testosterone replacement therapy. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*, *13*(2), 75-80.

Phan, K. L., Wager, T. D., Taylor, S. F., & Liberzon, I. (2004). Functional neuroimaging studies of human emotions. *CNS spectrums*, *9*(4), 258-66.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Current opinion in neurobiology*, *14*(2), 198-202.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological psychiatry*, *54*(5), 504-14.

Pompili, A., Arnone, B., & Gasbarri, A. (2012). Estrogens and memory in physiological and neuropathological conditions. *Psychoneuroendocrinology*, *37*(9), 1379-96.

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *NeuroImage*, *51*(2), 501-11.

Redondo, R. L., & Morris, R. G. M. (2011). Making memories last: the synaptic tagging and capture hypothesis. *Nature reviews Neuroscience*, *12*(1), 17-30.

Ribases, M., Gratacos, M., Badia, A., Jimenez, L., Solano, R., Vallejo, J., Fernandez-Aranda, F., et al. (2005). Contribution of NTRK2 to the genetic susceptibility to anorexia nervosa, harm avoidance and minimum body mass index. *Molecular psychiatry*, *10*(9), 851-60.

Rodrigues, S. M., Schafe, G. E., & LeDoux, J. E. (2004). Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. *Neuron*, *44*(1), 75-91.

Roozendaal, B., & McGaugh, J. L. (2011). Memory modulation. *Behavioral neuroscience*, *125*(6), 797-824.

Roselli, C. E., Klosterman, S., & Resko, J. A. (2001). Anatomic relationships between aromatase and androgen receptor mRNA expression in the hypothalamus and amygdala of adult male cynomolgus monkeys. *The Journal of comparative neurology*, *439*(2), 208-23.

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and biobehavioral reviews*, *39C*, 34-50.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., Beck, S., et al. (2011). Emotional perception: meta-analyses of face and natural scene processing. *NeuroImage*, *54*(3), 2524-33.

Sarkey, S., Azcoitia, I., Garcia-Segura, L. M., Garcia-Ovejero, D., & DonCarlos, L. L. (2008). Classical androgen receptors in non-classical sites in the brain. *Hormones and behavior*, *53*(5), 753-64.

Sarrieau, A., Mitchell, J. B., Lal, S., Olivier, A., Quirion, R., & Meaney, M. J. (1990). Androgen binding sites in human temporal cortex. *Neuroendocrinology*, *51*(6), 713-6.

Schacter, D. L., & Buckner, R. L. (1998). Priming and the brain. *Neuron*, *20*(2), 185-95.

Sen, P. N., & Basser, P. J. (2005). A model for diffusion in white matter in the brain. *Biophysical journal*, *89*(5), 2927-38.

Shapiro, M. (2001). Plasticity, hippocampal place cells, and cognitive maps. *Archives of neurology*, *58*(6), 874-81.

Simerly, R. B., Chang, C., Muramatsu, M., & Swanson, L. W. (1990). Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *The Journal of comparative neurology*, *294*(1), 76-95.

Spalek, K., Fastenrath, M., Ackermann, S., Auschra, B., Coynel, D., Frey, J., Gschwind, L., et al. (in preparation (a)). Gender-dependent dissociation between emotional perception and memory: a large–scale behavioural and fMRI study.

Spalek, K., Coynel, D., Fastenrath, M., Freytag, V., Heck, A., Milnik, A., Vukojevic, V., et al. (in preparation (b)). Genetic variants of NTRK2 are associated with emotion processing, a white-matter measure and DNA methylation levels in healthy young subjects.

Squire, L. R. (1986). Mechanisms of memory. *Science*, *232*(4758), 1612-9.

Squire, L. R. (1987). The organization and neural substrates of human memory. *International journal of neurology*, *21-22*, 218-22.

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological review*, *99*(2), 195-231.

Squire, L. R. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiology of learning and memory*, *82*(3), 171-7.

Squire, L. R., & Kandel, E. R. (2009). *Memory. From Mind to Molecules* (second edition). Greenwood Village: Roberts and Company Publishers.

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annual review of neuroscience*, *34*, 259-88.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(24), 13515-22.

Squire, L. R., & Zola, S. M. (1998). Episodic memory, semantic memory, and amnesia. *Hippocampus*, *8*(3), 205-11.

Stanton, S. J., Wirth, M. M., Waugh, C. E., & Schultheiss, O. C. (2009). Endogenous testosterone levels are associated with amygdala and ventromedial prefrontal cortex responses to anger faces in men but not women. *Biological psychology*, *81*(2), 118-22.

Stevens, J. S., & Hamann, S. (2012). Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. *Neuropsychologia*, *50*(7), 1578-93.

Strauss, G. P., & Herbener, E. S. (2011). Patterns of emotional experience in schizophrenia: differences in emotional response to visual stimuli are associated with clinical presentation and functional outcome. *Schizophrenia research*, *128*(1-3), 117-23.

Sun, M.-K., & Alkon, D. L. (2014). The "memory kinases": roles of PKC isoforms in signal processing and memory formation. *Progress in molecular biology and translational science*, *122*, 31-59.

Sundram, F., Deeley, Q., Sarkar, S., Daly, E., Latham, R., Craig, M., Raczek, M., et al. (2012). White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex; a journal devoted to the study of the nervous system and behavior*, *48*(2), 216-29.

Sweatt, J. D. (2013). The emerging field of neuroepigenetics. *Neuron*, *80*(3), 624-32.

Taylor, S. F., Phan, K. L., Decker, L. R., & Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. *NeuroImage*, *18*(3), 650-9.

Thilers, P. P., Macdonald, S. W. S., & Herlitz, A. (2006). The association between endogenous free testosterone and cognitive performance: a population-based study in 35 to 90 year-old men and women. *Psychoneuroendocrinology*, *31*(5), 565-76.

Todd, R. M., Palombo, D. J., Levine, B., & Anderson, A. K. (2011). Genetic differences in emotionally enhanced memory. *Neuropsychologia*, *49*(4), 734-44.

Travers, B. G., Adluru, N., Ennis, C., Tromp, D. P. M., Destiche, D., Doran, S., Bigler, E. D., et al. (2012). Diffusion tensor imaging in autism spectrum disorder: a review. *Autism research : official journal of the International Society for Autism Research*, *5*(5), 289-313.

Uzefovsky, F., Shalev, I., Israel, S., Knafo, A., & Ebstein, R. P. (2012). Vasopressin selectively impairs emotion recognition in men. *Psychoneuroendocrinology*, *37*(4), 576-80.

Wang, K., Li, M., & Hakonarson, H. (2010). Analysing biological pathways in genome-wide association studies. *Nature reviews Genetics*, *11*(12), 843-54.

Waugh, C. E., Hamilton, J. P., & Gotlib, I. H. (2010). The neural temporal dynamics of the intensity of emotional experience. *NeuroImage*, *49*(2), 1699-707.

Weinstock, L. S. (1999). Gender differences in the presentation and management of social anxiety disorder. *The Journal of clinical psychiatry*, *60 Suppl 9*, 9-13.

Wetmore, C., Ernfors, P., Persson, H., & Olson, L. (1990). Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by in situ hybridization. *Experimental neurology*, *109*(2), 141-52.

Wirth, M. M., Stanton, S. J., Gaffey, A. E., & Liening, S. H. (2012). Letter in response to Ackermann et al., "Testosterone levels in healthy men are related to amygdala reactivity and memory performance". *Psychoneuroendocrinology*, *37*(9), 1587-8.

Wolf, O. T., & Kirschbaum, C. (2002). Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Hormones and behavior*, *41*(3), 259-66.

Wolf, O. T., Kuhlmann, S., Buss, C., Hellhammer, D. H., & Kirschbaum, C. (2004). Cortisol and memory retrieval in humans: influence of emotional valence. *Annals of the New York Academy of Sciences*, *1032*, 195-7.

Xu, C., Liu, Q.-Y., & Alkon, D. L. (2014). PKC activators enhance GABAergic neurotransmission and paired-pulse facilitation in hippocampal CA1 pyramidal neurons. *Neuroscience*, *268*, 75-86.

Yonker, J. E., Eriksson, E., Nilsson, L.-G., & Herlitz, A. (2006). Negative association of testosterone on spatial visualization in 35 to 80 year old men. *Cortex; a journal devoted to the study of the nervous system and behavior*, *42*(3), 376-86.

Young, K. D., Bellgowan, P. S. F., Bodurka, J., & Drevets, W. C. (2013). Functional neuroimaging of sex differences in autobiographical memory recall. *Human brain mapping*, *34*(12), 3320-32.

Young, L. A., Neiss, M. B., Samuels, M. H., Roselli, C. E., & Janowsky, J. S. (2010). Cognition is not modified by large but temporary changes in sex hormones in men. *The Journal of clinical endocrinology and metabolism*, *95*(1), 280-8.

Zanetti, M. V., Jackowski, M. P., Versace, A., Almeida, J. R. C., Hassel, S., Duran, F. L. S., Busatto, G. F., et al. (2009). State-dependent microstructural white matter changes in bipolar I depression. *European archives of psychiatry and clinical neuroscience*, *259*(6), 316-28.

Zeng, H., Chattarji, S., Barbarosie, M., Rondi-Reig, L., Philpot, B. D., Miyakawa, T., Bear, M. F., et al. (2001). Forebrain-specific calcineurin knockout selectively impairs bidirectional synaptic plasticity and working/episodic-like memory. *Cell*, *107*(5), 617-29.

van Ast, V. A., Cornelisse, S., Marin, M.-F., Ackermann, S., Garfinkel, S. N., & Abercrombie, H. C. (2013). Modulatory mechanisms of cortisol effects on emotional learning and memory: novel perspectives. *Psychoneuroendocrinology*, *38*(9), 1874-82.

van Wingen, G. A., Ossewaarde, L., Bäckström, T., Hermans, E. J., & Fernández, G. (2011). Gonadal hormone regulation of the emotion circuitry in humans. *Neuroscience*, *191*, 38-45.

DECLARATION BY CANDIDATE

I declare herewith that I have independently carried out the PhD – thesis entitled „Sex dependency and genetic modulation of emotional processing and memory: a behavioural and imaging study“. This thesis consists of original research articles that have been written in cooperation with the enlisted co-authors and have been published in peer-reviewed scientific journals or are in preparation for publication / submitted for publication. Only allowed resources were used and all references used were cited accordingly.

Date: 23. May 2014

Signature: