

The Psychophysiology of Posttraumatic Stress
Disorder and Panic Disorder: Fear Conditioning,
Autonomous Underpinnings and Issues of
Measurement

Die Psychophysiologie der Posttraumatischen
Belastungsstörung und der Panikstörung:
Furchtkonditionierung, autonome Grundlagen und
methodologische Aspekte ihrer Messung

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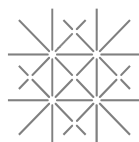
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Widmung und Danksagung

Eine Arbeit von diesem Umfang ist immer eine gemeinsame Leistung. Und zwar von Menschen, die nur zum kleineren Teil als Mitautoren erscheinen. Zunächst möchte ich den Menschen danken, die die größten Opfer für die Erstellung dieser Arbeit geleistet haben: meiner Tochter Lou Mayla, die mich in den ersten Lebenswochen viel zu wenig zu Gesicht bekam und meiner Freundin Julia Wörner, die mir den Rücken freigehalten hat, und den Glauben an bessere Zeiten nicht aufgegeben hat.

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Erklärung über die Selbstständigkeit

Die zur Promotion eingereichten Zeitschriftenbeiträge wurden in Zusammenarbeit mit den jeweiligen Koautoren angefertigt. Es handelt sich dabei um Originalarbeiten, die bei Zeitschriften zur Veröffentlichung eingereicht wurden. Diese Arbeiten wurden weder von den Beteiligten noch von anderen Personen an anderer Stelle veröffentlicht. Es wurden nur die angegebenen Hilfsmittel benutzt und alle Zitate sind gekennzeichnet.

Basel, den 24.10.06

A handwritten signature in black ink, appearing to read 'Jens Blechert'. The signature is written in a cursive style with a large initial 'J' and a long horizontal stroke at the end.

Jens Blechert

Zusammenfassung

Die Ergründung des Phänomens Angst in seinen gesunden und pathologischen Ausprägungen stellt für Forscher und Kliniker auch nach Jahrzehnten intensiver Forschung immer noch eine Herausforderung dar. Angst ist eine adaptive und verhaltenssteuernde Emotion, die physiologische, affektive und kognitive Reaktionsebenen umfasst. Die vorliegende Arbeit beinhaltet vier Studien zu methodischen Aspekten der Messung von Angst, ihrem Erwerb sowie zu den zugrunde liegenden physiologischen Mechanismen.

Die Psychophysiologie ermöglicht die Erfassung einer Vielzahl autonomer und respiratorischer Prozesse, die bei der Emotionsexpression beteiligt sind. Die Studie STATE untersuchte bei einer gesunden Stichprobe, welche dieser Prozesse von einer Angstinduktion beeinflusst werden. Um auch klinische Ausprägungen von Angst zu untersuchen, wurden Patienten mit Posttraumatischer Belastungsstörung (PTSD) und Panikstörung (PD) sowie gesunde Kontrollprobanden hinsichtlich dieser Prozesse verglichen.

Moderne Konditionierungstheorien erklären die Entstehung klinischer Angst mit Hilfe assoziativer Lernmechanismen und kognitiver Prozesse. Klinische Studien zur Furchtkonditionierung sind jedoch rar. Zudem lassen bisherige Paradigmen zur Konditionierung autonomer Maße dass die Erfassung kognitiver und affektiver Prozesse nicht zu. Die Studie RATE untersuchte, ob sich solche Messungen in ein Konditionierungsparadigma integrieren lassen und ob affektive Prozesse eine andere Lernkurve aufweisen als autonome Maße. Die Studie RATE legte damit die Grundlage für die FCP Studie, welche die Konditionierbarkeit von PTSD Patienten untersuchte.

Die Ergebnisse der Studie STATE zeigten, dass eine Vielzahl autonomer und respiratorischer Parameter zur Indizierung von Angst geeignet ist. Dies wurde in der PASS Studie repliziert und auf zwei klinische Gruppen übertragen: die PTSD Gruppe zeigte ein Muster von Überaktivierung des sympathischen Nervensystems bei gleichzeitiger Unteraktivierung des parasympathischen Nervensystems. PD Patienten zeigten hauptsächlich respiratorische Auffälligkeiten.

Die RATE Studie belegte, dass kognitive und affektive Prozesse in der Furchtkonditionierung eine wichtige Rolle spielen und sich deren Messung gut in das Furchtkonditionierungsparadigma integrieren lässt. Die FCP Studie erbrachte Hinweise auf ein pathogenes Konditionierungsmuster der PTSD Patienten: sie zeigten Defizite bei der Löschung konditionierter Furchtreaktionen auf autonomen, affektiven und kognitiven Maßen.

Implikationen für Diagnostik, Verhaltensgenetik und differenzielle Therapieindikation werden diskutiert.

1 Allgemeine Einleitung¹

Mit einer Lebenszeitprävalenz von 29% sind Angststörungen mittlerweile die am weitesten verbreitete Klasse psychischer Störungen (Kessler et al., 2005). Gegenüber Zahlen von 1994 (19%) ist die Häufigkeit damit deutlich angestiegen (Kessler et al., 1994). Die Posttraumatische Belastungsstörung (posttraumatic stress disorder, PTSD) ist nach spezifischen und sozialen Phobien mit 6.8% Lebenszeitprävalenz die dritthäufigste Angststörung in den USA. Die Untersuchung von klinischen und nichtklinischen Angstzuständen hat von daher eine hohe Relevanz sowohl für die Gesundheitsversorgung (Simon, Ormel, VonKorff, & Barlow, 1995) als auch für das grundlegende Verständnis menschlicher Emotionen (Barlow, 2000).

Angst ist ein komplexes Phänomen, welches heute übereinstimmend auf drei Ebenen beschrieben wird: auf der verbal-kognitiven, der psychophysiologisch/emotionalen, und der Verhaltensebene (z.B. Lang, 1978; Pauli, Rau, & Birbaumer, 2000). Im Gegensatz zur bisher angenommenen koordinierten Aktivierung aller drei Ebenen durch intensive Emotionen hat die Forschung vielfach eine Diskordanz der Ebenen gefunden, z.B. ein verbaler Bericht von erlebter Angst, ohne physiologische Aktivierung (Wilhelm & Roth, 2001). Patienten mit Angststörungen berichten vielfach über überschießende und als bedrohlich wahrgenommene körperliche Symptome wie z.B. Herzrasen oder Atmennot bei Panikstörung (panic disorder, PD) oder Schlafstörungen und Schreckhaftigkeit bei Posttraumatischer Belastungsstörung (posttraumatic stress disorder, PTSD) welche daraufhin als diagnostische Kriterien in das DSM-IV aufgenommen wurden. Trotz der häufig gefundenen Diskordanz von Physiologie und Selbstbericht verlassen sich die gängigen diagnostischen Verfahren auf letzteren. Ein Grund dafür könnte sein, dass es der Forschung bis heute nicht gelungen ist, den diagnostischen Kategorien eindeutige psychophysiologische Profile zuzuordnen oder verlässliche Verhaltensvorhersagen zu machen (Orr & Roth, 2000; Wilhelm & Roth, 2001).

Die, auf Selbstbericht basierende Diagnostik definiert sehr breite und heterogene Störungskategorien. Das hat zur Folge, dass neue Forschungszweige wie Verhaltensgenetik nur niedrige bis moderate Zusammenhänge zwischen genetischen Markern bzw. molekularen Mechanismen und psychiatrischer Diagnose finden. Es wurde daraufhin vorgeschlagen, psychophysiologische Eigenschaften/Profile der einzelnen Störungen als „Zwischenstufe“

¹ Um die Lesbarkeit zu erleichtern, werden im Folgenden nur solche Referenzen angeführt, die nicht bereits in den einzelnen Artikel enthalten sind.

zwischen Genexpression und Verhalten zu definieren und deren Zusammenhänge mit genetischen Markern zu untersuchen. Dieses Konzept des Endophänotyps (zwischen Genotyp und Phänotyp) findet inzwischen vermehrt Verwendung (de Geus, 2002; Gottesman & Gould, 2003).

Die Diskrepanz zwischen physiologischen Messungen und subjektivem Erleben von Angst ist auch therapeutisch relevant. Beispielsweise läuft ein erheblicher Teil von Panikattacken ohne physiologische Aktivierung ab (z.B. Forsyth, Eifert, & Canna, 2000). Behandlungsansätze gehen aber von der Existenz solcher Aktivierung, bzw. von der Wahrnehmung von körperlicher Aktivierung aus (Clark, 1999) und psychopharmakologische Medikation ist häufig auf die Reduktion physiologischer Symptome ausgerichtet. Aus dem Wissen über Existenz und Stärke der physiologischen Aktivierung bei berichteter Angst ließe sich auch eine differenzielle Behandlungsindikation ableiten (Ost, Jerremalm, & Johansson, 1981; Pauli et al., 2000).

Umfangreiche Verbesserungen in psychophysiologischen Messmethoden und ein vertieftes Verständnis der physiologischen Zusammenhänge (Berntson, Cacioppo, & Quigley, 1993) führten zur Falsifizierung bzw. Verfeinerung vieler singulärer biopsychologischer Angsttheorien (Roth, 2005) und zu einer umfassenderen Betrachtung zugrunde liegender physiologischer Prozesse. Vor allem die Auswahl, Messung und Verarbeitung psychophysiologischer Information hat sich als entscheidend für klinische Schlussfolgerungen und für die Genauigkeit von Klassifikationen herausgestellt.

Die Studie „Psychophysiologische Indexierung von State Angst“, **STATE** untersucht eine umfangreiche Batterie von innovativen psychophysiologischen Messmethoden bezüglich ihrer Sensitivität für State-Angst und leitet methodologische Empfehlungen ab. State-Angst wurde in einer „threat of shock“ Phase induziert, in der eine elektrische Stimulation angekündigt, jedoch nicht appliziert wurde. Dieser Angstphase ging eine Ruhephase voraus.

Aufbauend auf der STATE Studie wurde ein Teil dieser Messmethoden auf zwei klinische Stichproben angewendet. Die Studie **Psychophysiologisches Assessment** von PTSD und PD, **PASS** ging von wiederholten Befunden kardiovaskulärer Dysregulation bei PTSD und respiratorischer Dysregulation bei PD aus. Um diese Befunde zu replizieren und mit Hilfe von umfangreicheren Messungen besser zu verstehen, wurden daher PTSD Patienten, PD Patienten und gesunde Kontrollprobanden während einer fünf-minütigen Baseline-Phase („quiet-sitting baseline“) auf einer großen Bandbreite autonomer und respiratorischer Masse verglichen.

Während diese Art von „psychophysiologischer Profilierung“ das Verständnis aktueller Manifestationen psychiatrischer Störungen erhöht, können auf diese Weise jedoch keine ätiologischen Fragestellungen beantworten. Es gibt Hinweise, dass habituelle physiologische Aktivierungsmuster einerseits auf konstitutionelle, evt. genetisch determinierte Eigenschaften des Nervensystems hinweisen, andererseits aber auch potenten *Lernmechanismen* unterliegen. Klassisches Konditionieren wurde als Erklärungsmodell z.B. für die Hyperreaktivität auf störungsspezifische Reize angeführt. Die automatische und unwillkürliche Assoziation eines biologisch relevanten Reizes (unkonditionierter Stimulus, US) mit einem neutralen konditionierten Reize (konditionierter Reiz, CS) kann die Irrationalität vieler Ängste erklären, bei denen es den Betroffenen häufig selbst schwer fällt, ihre Reaktionen zu verstehen. Die älteren, statischen Konditionierungsmodelle (z.B. Marks, 1969; Mowrer, 1960) konnten jedoch viele klinische Phänomene nicht erklären, wie z.B. die Entwicklung von Phobien ohne traumatische Erfahrungen mit dem phobischen Objekt (fehlender US) und wurden daher vielfach kritisiert (z.B. Aitken, Lister, & Main, 1981).

Weiterentwicklungen der ursprünglichen Konditionierungsmodelle konnten einen Grossteil der Kritikpunkte aufnehmen, insbesondere durch die Berücksichtigung von kognitiven Variablen (Davey, 1997; Vriends, Michael, & Margraf, 2005). Zudem konnte die Integration von Befunden zum *Evaluativen Konditionieren* (Baeyens & De Houwer, 1995) einige Inkonsistenzen aufklären. *Evaluatives Konditionieren*, welches als separater Prozess während der klassischen Konditionierung abläuft, beschreibt die Übertragung der Valenz eines US auf einen CS. Komplementär zum evaluativen Lernen versteht man unter *Signallernen* einen Prozess, durch den der CS zum Signal (Prädiktor) für den US wird und welcher meist mit psychophysiologischen Parametern gemessen wird. Klassisches Konditionieren beinhaltet also zwei Prozesse: evaluatives Lernen und Signallernen.

Ein typisches differenzielles Konditionierungsparadigma umfasst drei Phasen: eine Habituationsphase, während der zwei Stimuli in wechselnder Reihenfolge dargeboten werden, eine Akquisitionsphase, während der einer der Stimuli (CS+) vom US gefolgt wird, und eine Extinktionsphase, in der wiederum beide CS ungepaart dargeboten werden. Der grundlegende Ablauf eines solchen Konditionierungsparadigmas ist im Anhang, Graphik 1 angefügt. Dieses Untersuchungsparadigma ist jedoch auf die Messung psychophysiologischer Variablen abgestimmt, und eine Prozedur zur parallelen Untersuchung der beiden Lernprozesse evaluatives Lernen und Signallernen fehlte.

Studie **RATE** untersuchte, ob sich mittels wiederholter Ratingprozeduren während eines klassischen Konditionierungsparadigmas evaluatives Lernen messen lässt. Eine Gruppe

von Probanden gab während der Konditionierung wiederholt Valenzratings ab, während eine zweite Gruppe dies nicht tat, um zu überprüfen, wie diese Ratings den Verlauf psychophysiologischer Indikatoren (das Signallernen) beeinflussen (siehe Graphik 2 im Anhang). Als weitere Fragestellung wurde untersucht, ob diese Valenzbewertungen lösungsresistenter sind als die psychophysiologischen Messungen. Nach der Theorie des Evaluativen Lernens sollten Valenzbewertungen (evaluatives Lernen) löschesistenter sein als elektrodermale Reaktionen (Signallernen).

Ausgehend von den Ergebnissen der RATE-Studie wurde dieses neu entwickelte Paradigma an den zwei Patientengruppen angewendet, die schon an Studie PASS teilgenommen hatten. Gesunde und traumatisierte Probanden dienten als Kontrollgruppen für die PD bzw. PTSD Patienten. Neben psychophysiologischen Messungen wurden nun erstmals auch Valenzratings und US-expectancy ratings sowie ein Verhaltenstest eingesetzt, um die Furchtkonditionierung auf allen relevanten Ebenen adäquat zu erfassen. Zur Panikstörung existierten noch keine Konditionierungsstudien und vorige Studien von Konditionierbarkeit bei PTSD hatten bisher nur psychophysiologische Variablen untersucht. Die Resultate wurden in zwei Publikationen veröffentlicht (Blechert, Michael, & Wilhelm, submitted; Michael, Blechert, Vriends, Margraf & Wilhelm, submitted) von denen erstere Bestandteil dieser Dissertation ist : Fear Conditioning in PTSD (Studie FCP)

2 Fragestellungen

Die vorliegenden Studien haben sowohl klinische Fragestellungen (Studien FCP und PASS) als auch methodische Fragestellungen (Studien STATE und RATE) untersucht:

- Sind verschiedene respiratorische und autonome Variablen sensitiv für STATE-Angst? Wie gut beschreiben tonische Masse und Variabilitätsmasse STATE-Angst, sowohl individuell als auch in Kombination?
 - > Studie **STATE**
- Gibt es störungsspezifische, autonome und respiratorische Aktivierungsmuster in PTSD resp. PD ?
 - > Studie **PASS**
- Lassen sich kognitive und psychophysiologische Prozesse parallel in einem aversiven Konditionierungsparadigma messen? Ist Evaluatives Lernen löschresistenter als Signallernen?
 - > Studie **RATE**
- Ist die Konditionierbarkeit bei PTSD Patienten erhöht? Zeigen kognitive Variablen ebenfalls PTSD-spezifische Konditionierungseffekte?
 - > Studie **FCP**

3 Die Studien

Die Studien sind farbcodiert und in folgender Reihenfolge angefügt:

- Studie STATE** Blechert, J., Lajtman, M., Michael, T., Margraf, J., & Wilhelm, F. H. (2006). Identifying anxiety states using broad sampling and advanced processing of peripheral physiological information. *Biomedical Sciences Instrumentation*, 42, 136-141.
- Studie PASS** Blechert J., Michael T., Grossman, P., Lajtman M., Wilhelm F.H. (submitted). Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosomatic Medicine*.
- Studie RATE** Blechert, J., Michael, T., Williams, L. S., & Wilhelm, F. H. (submitted). When two paradigms meet: does evaluative learning extinguish in differential fear conditioning? *Cognition and Emotion*.
- Studie FCP** Blechert, J., Michael, T., & Wilhelm, F. H. (under review). Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomous, experiential, and behavioral measures. *Behaviour Research and Therapy*.

Im Anhang sind Graphiken angeführt, welche die Designs der Studien FCP und RATE veranschaulichen.

4 Zusammenfassende Diskussion

Zunächst werden die Studienergebnisse zusammengefasst und übergreifend interpretiert. Anschließend werden Schlussfolgerungen gezogen, die über die aktuellen Studienergebnisse hinausgehen, um diese in einen umfassenderen Gesamtzusammenhang zu stellen. Es sei darauf hingewiesen, dass diese übergreifenden Konzepte hypothetisch sind. Sie dienen dem Ziel, die Studien, welche unter der Benutzung unterschiedlicher Paradigmen Fragestellungen auf verschiedenen Ebenen beantworten, auf der übergreifenden Ebene zu synthetisieren. Dabei wurde besonders auf therapeutische Implikationen eingegangen.

4.1 Die Studienergebnisse

Studie *STATE* untersuchte die Sensitivität psychophysiologischer Masse bzgl. der Unterscheidung einer Ruhephase von einer State-Angst Phase (angedrohter elektrischer Reiz). Die Ergebnisse zeigten hohe Effektstärken für elektrodermale und behaviorale Variablen und mittlere bis niedrige Effektstärken für respiratorische und kardio-vaskuläre Messungen. Einige Beispiele für Effektstärken waren: Hautleitfähigkeitslevel (skin conductance level, SCL): 0.86, Pulswellenamplitude: 0.76, respiratorische Rate: 0.78, end-titales partielles CO₂ (pCO₂): 0.33, Herzrate (HR): 0.29. Basieren auf den Werten der sechs sensitivsten Variablen konnte eine Diskriminanzanalyse eine zu 83% korrekte Klassifikation der zwei Phasen machen. Überraschend niedrig waren die Effektstärken für respiratorische Sinusarrhythmie (RSA) und T-Wellen Amplitude. Diese Effekte wurden jedoch in einem within-subject Design errechnet und könnten in einem between-subject Design höhere Effektstärken erbringen. Insbesondere bei der RSA sollte klar zwischen between und within subjects Analysen unterschieden werden, und experimentell bedingte Veränderungen von Atmungsparametern in die Kalkulation von RSA mit einbezogen werden (Grossman & Kollai, 1993; Grossman & Taylor, in press; Ritz & Dahme, 2006).

Basierend auf diesen Ergebnissen und vorliegenden klinischen Studien wurden einige dieser Variablen als primäre Indikatoren für die Studie *PASS* ausgewählt (z.B. HR, SCL, RSA, pCO₂). Als sekundäre Variablen wurde zudem eine Reihe respiratorischer Variablen gemessen, welche in der STATE Studie hohe Effektstärken erbracht hatten. Bzgl. dieser Variablen wurden PTSD und PD Patienten während 5-minütigem ruhigen Sitzens miteinander und mit gesunden Kontrollprobanden verglichen. Entsprechend den Erwartungen zeichneten

sich die PTSD Patienten im Vergleich zu PD Patienten und gesunden Kontrollen durch eine niedrige RSA aus. Im Gegensatz zu vorigen Studien wurde in der PASS Studie erstmals auch eine Reihe potentiell konfundierter Variablen bei der Bestimmung der RSA berücksichtigt. Erwartungsgemäß zeigten PTSD Patienten auch eine höhere HR, sowie erhöhtes elektrodermales Arousal. Ein zusammengesetzter Index aus Pulswellen-Amplitude und Pulswellen-Geschwindigkeit, sowie T-Wellen Amplitude wies auf einen signifikant erhöhten kardialen Sympathikotonus bei beiden Patientengruppen hin. PTSD Patienten zeigten also ein Aktivierungsmuster, welches von reduzierter Parasympathikusaktivierung und verstärkter Sympathikusaktivierung gekennzeichnet war. Die Gruppe der Panikpatienten war insgesamt unauffälliger, einzig das niedrige pCO₂ war spezifisch für diese Gruppe. Dieser Zustand von „hypercapnia“ wurde schon wiederholt in dieser Patientengruppe gefunden und oftmals mit Hyperventilation oder tiefen Seufzern in Verbindung gebracht. Dieses Respirationsmuster war bei den PD Patienten jedoch nicht ersichtlich. Dafür wurde überraschenderweise eine erhöhte Anzahl tiefer Seufzer in der PTSD Gruppe gefunden.

Studie **RATE** erbrachte den wichtigen Befund, dass die kontinuierliche Messung von Valenzveränderungen der Stimuli während einem typischen klassischen Konditionierungsparadigmas die elektrodermalen Konditionierung nicht wesentlich beeinflusst. Zudem konnte die lerntheoretisch wichtige Unterscheidung von evaluativem Lernen (Valenzbewertungen) und Signallernen (Hautleitfähigkeitsreaktionen, SCRs) überprüft werden: die Valenzbewertungen löschten während der Extinktionsphase langsamer als die SCRs. Im Unterschied zu vorigen Studien konnte dies auch mit Stimuli gezeigt werden, welche eine spontane Bewertung auslösen (farbige Tintenklecksbilder).

Die Studie RATE stellte damit eine wichtige Grundlage für die **FCP** Studie dar, welche von dem Verfahren der Valenzratings Gebrauch machte, und zudem noch subjektive Ratings von US-Erwartung (US-expectancy) in das Konditionierungsparadigma integrierte. Diese verbal-kognitiven Variablen ermöglichten erstmals einen Einblick in die kognitiv-affektiven Lernprozesse von PTSD Patienten während der Furchtkonditionierung.

Die Ergebnisse der FCP Studie bestätigten und ergänzten vorherige Studienresultate. PTSD Patienten zeigten eine generell erhöhte Reaktivität auf alle Reize. Das *differenzielle* Konditionierungsparadigma kann eine generelle Hyperreaktivität von assoziativem Lernen unterscheiden: der CS+ wird während der Akquisitionsphase mit den US gepaart, während der CS- immer ungepaart präsentiert wird. Hyperreaktivität sollte sich bei beiden CS-Typen

zeigen. Ist die Reaktivität jedoch selektiv auf den CS+ erhöht, schließt man auf assoziatives Lernen durch die Koppelung des CS+ mit dem US in der Akquisitionsphase. In der FCP Studie zeigte sich neben Hyperreaktivität auch ein Unterschied im assoziativen Lernen während der Extinktionsphase: PTSD Patienten reagierten elektrodermal stärker und länger auf den CS+ als gesunde Kontrollprobanden, bei denen diese Reaktionen schnell löschten. Dieser Gruppenunterschied lag beim CS- nicht vor. Die Valenzratings zeigten ein ähnliches Muster: im Vergleich zu gesunden Probanden gaben PTSD Patienten generell negativere Valenzbewertungen für beide CS-Typen ab. Ähnlich wie bei den elektrodermalen Reaktionen, und reduzierten PTSD Patienten die negative Bewertung während der Extinktionsphase nicht in gleichem Masse wie die Kontrollprobanden. Beim CS+ war dieser „delayed-extinction“ Effekt besonders ausgeprägt. Ebenfalls sehr deutlich waren die Gruppenunterschiede bei den Ratings der US-expectancy. Die Erwartung, dass auf den CS+ der US folgt war am Ende der Akquisitionsphase in beiden Gruppen am höchsten. Die gesunden Probanden reduzierten diese Erwartung während der Extinktionsphase deutlich, PTSD Patienten hingegen gaben nach der Extinktionsphase sogar noch leicht erhöhte US-Erwartung an, d.h. sie rechneten fest mit einer weiteren Darbietung des elektrischen US. Zusem hatten die PTSD Patienten Schwierigkeiten beim Erlernen der CS-US Kontingenz: 33% der PTSD Patienten, aber nur 12% der Kontrollprobanden konnten den CS+ nach der Extinktion nicht (mehr) korrekt identifizieren.

Diese Befunde stimmen mit Theorien überein, welche verzögerte Löschung als pathogen für Angststörungen ansehen und rechtfertigen das Rational von Konfrontationstherapien, welche von diesem defizitären Extinktionslernen ausgehen. Sie sind auch interessant im Zusammenhang mit neueren theoretische Arbeiten, die auf die Funktionalität des Kontingenzlernens hinweisen (Grillon, 2002). Demnach erhöht differenzielles Lernen die Vorhersagbarkeit aversiver Konsequenzen. Differenzielle Konditionierungsparadigmen erzeugen kurze, phasische Furchtreaktionen, welche auf einen bestimmten Reiz bezogen sind und *reduzieren* dadurch tonische, lang anhaltende Angst. Dazu passt der Befund der FCP Studie, dass ein erheblicher Teil der PTSD Patienten Schwierigkeiten im Kontingenzlernen hat. Auch weist diese Argumentation daraufhin, dass die *Akquisition* von Furcht funktional ist, da es die Vorhersagbarkeit negativer Konsequenzen erhöht. Nur das Fehlen einer *Extinktion* von Furchtreaktionen ist als pathogen anzusehen.

Die ACP Studie ging somit in mehrerer Hinsicht über frühere Studien hinaus. Neben methodischen Vorteilen wie einer vergleichsweise großen PTSD-Stichprobe mit zwei Kontrollgruppen war es die erste Studie, die bei PTSD Patienten auch affektives und kognitives Lernen (Ratings von Valenz und US-Erwartung) erfasste. Die Integration von

kognitiven Variablen in ein psychophysiologisches Konditionierungsparadigma macht es einerseits möglich, Parallelen zu kognitiven Paradigmen zu ziehen. Andererseits wirft es die Frage über die Ursache der beobachteten Konditionierungsmuster auf. Wenn Furchtkonditionierung Effekte auf physiologische (implizite) und verbal-kognitive (explizite) Systeme zeigt und PTSD Patienten sich auf beiden Ebenen von Gesunden unterscheiden stellt sich die Frage der Kausalität. So wäre denkbar, dass sich ein kognitiver Erwartungsbias (Überschätzung negativer Konsequenzen) den Gruppenunterschieden zu Grunde liegt, der sich auch auf Valenzbewertungen und elektrodermale Reaktionen auswirkt. Alternativ könnte es sein, dass das subkortikale Furchtsystem von PTSD Patienten anders lernt, und dass dieser implizite Prozess sich auch in einem expliziten Erwartungsbias zeigt.

4.2 *Mind or Body? Explizite und implizite Konditionierungsprozesse*

Biologisch orientierte Konditionierungstheorien von PTSD führen die Symptome des Hyperarousals und des Wiedererlebens auf *implizite* Assoziation der Furchtreaktion während der Traumatisierung mit Umgebungsreize zurück (Orr et al., 2000; Rothbaum & Davis, 2003). Die Studie ACP zeigte jedoch, dass sich PTSD-spezifische Defizite auf *expliziter* Ebene zeigen. Verbale Ratings von US-erwartung und Stimulusvalenz zeigten ähnliche Verläufe wie elektrodermale Parameter. Dies weist auf eine prominente Rolle von kognitiven Prozessen bei der Furchtkonditionierung hin. Im Gegensatz zur modernen Konditionierungstheorie der Phobien (Davey, 1997) haben Konditionierungsmodelle der PTSD diese kognitiven Prozesse bisher nicht berücksichtigt. Ein integriertes Ätiologiemodell der PTSD sollte auch die Frage beantworten, ob die Ursache abnormer Konditionierungsprozesse auf einer *impliziten* (affektives Lernen: Valenzratings, elektrodermale Reaktionen) oder *expliziten* (US-Erwartung, Kontingenzwissen) Ebene liegt.

Lovibond und Shanks (2002) gehen davon aus, dass explizites Wissen um die CS-US Kontingenz die Voraussetzung für elektrodermale Konditionierung ist. Dem stehen neuere neurobiologische Konditionierungsmodelle gegenüber: Hamm und Kollegen gehen davon aus, dass Furchtkonditionierung auf zwei Ebenen abläuft: zum einen führt Furchtkonditionierung zum Erwerb von Kontingenzwissen (Wissen um die CS-US Koppelung). Zum anderen aktiviert dieses Paradigma auch ein amygdala-basiertes Furchtsystem, welches unabhängig von der kognitiven Verarbeitung lernt (Hamm & Weike,

2005). Diese konditionierten Reaktionen sind jedoch nur auf implizite Weise messbar wie z.B. durch den furchtpotenzierten Lidschlagreflexes (fear potentiated eyeblink startle)².

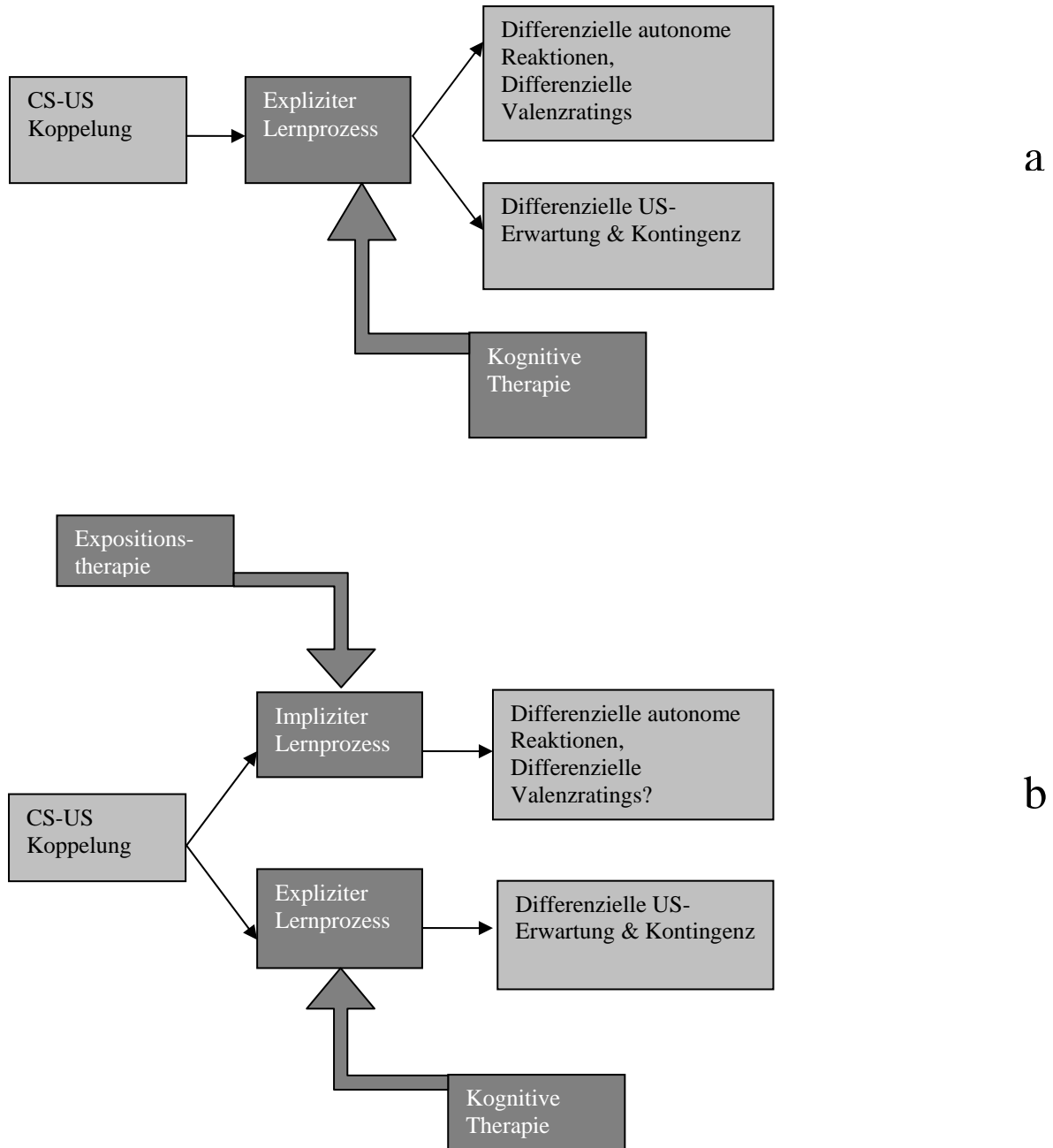
Graphik 3 kontrastiert diese beiden Modelle. Model (a) geht davon aus, dass Konditionierung primär in Form eines expliziten Lernprozesses abläuft, welcher die Reaktionen auf autonomer, affektiver und kognitiver Ebene steuert. Model (b) nimmt zwei parallele Mechanismen an: ein expliziter Mechanismus, welcher US-Erwartungen und Kontingenzlernen steuert, sowie einen impliziten Mechanismus, welcher psychophysiologische Reaktionen und eventuell auch affektive Bewertungen bedingt (siehe Baeyens, Hermans, & Eelen, 1993).

4.3 Therapeutische Implikationen der Konditionierungsbefunde

Eine Klärung der Body-Mind Frage, d.h. ob implizit-autonome oder explizit-kognitive Prozesse bei den Furchassoziationen von PTSD Patienten dominieren, könnte auch therapeutische Implikationen haben. Expositions-basierte Verhaltenstherapien basieren auf Konditionierungsmodellen (z.B. Rothbaum & Davis, 2003). Eine aktuelle Debatte in der Therapieforschung bei PTSD behandelt die Frage, ob kognitive Therapie zusätzlich zu Expositionstherapien notwendig ist (z.B. Foa et al, 2005, Foa & Rauch). Expositionstherapie zielt auf die Hemmung konditionierter Furchreaktionen ab. Wenn sich PTSD Patienten also auf einer impliziten Ebene von Gesunden unterscheiden, z.B. in der Aktivität eines amygdala-basierten Furchsystems, so ist Expositionstherapie indiziert. Ist es jedoch ein kognitiver Bias, der verzerrte US-Erwartungen und erhöhte Konditionierbarkeit bedingt, so könnte Kognitive Therapie notwendig sein, um diese verzerrte negative Erwartungen auf rationaler Ebene zu reduzieren (siehe auch McNally, 1995). Entsprechend dieser Überlegungen wurde in die Modelle in Graphik 3 hypothetisch die Zugänglichkeit für Expositions- bzw. kognitive Therapie eingezeichnet.

² Hamm, Veitl und Kollegen interpretieren die differenzielle elektrodermale Reaktion primär als kognitive Variable („cognitive orienting“), während die Aktivierung des Furchsystems am besten anhand des furchtpotenzierten Lidschlagreflexes (fear potentiated eyeblink-startle) zu messen sei. In Umgehung dieser methodologischen Frage werden hier startle und elektrodermale Reaktionen als autonome, d.h. nicht bewusst steuerbare Variablen aufgefasst.

Graphik 3. Zwei Konditionierungsmodelle mit kausaler Rolle (a) eines expliziten Lernprozesses, der konditionierte Reaktionen auf den verschiedenen Ebenen steuert (b) eines expliziten *und* eines impliziten Lernprozesses der kognitive bzw. autonome konditionierte Reaktionen steuert, sowie die hypothetische Zugänglichkeit der beiden Modelle für Kognitive- bzw. Expositionstherapie.



Anmerkung. CS, Konditionierter Stimulus; US, unconditionierter Stimulus

4.4 Konditionierbarkeit: State oder Trait?

Konditionierungstheorien bei Angststörungen basieren z.T. auf der Annahme von interindividuellen Unterschieden bei der Konditionierbarkeit, einem „conditionability-trait“ (Davey, 1997; Orr et al., 2000). Erhöhte Konditionierbarkeit soll demnach keine Folge der Störung sein, sondern dieser ursächlich vorausgehen. Durch diese Annahme lässt sich erklären, warum nach einer Traumaexposition nur ein Teil der Betroffenen eine PTSD entwickelt und andere sich schnell wieder erholen. Erhöhte Konditionierbarkeit bei Ersteren könnte zur stärker ausgeprägten und länger anhaltenden konditionierten Reaktionen und damit zu einer PTSD führen.

Trait-Konditionierbarkeit ist bisher noch nicht näher definiert worden. Unterstützung für den Trait-Ansatz kommt von Zwillingsstudien, die eine moderate Heredität für elektrodermale Konditionierbarkeit gefunden haben (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003; Merrill, Steinmetz, Viken, & Rose, 1999) sowie von genetischen Studien, die biologische Marker für Konditionierbarkeit identifizieren konnten (Garpenstrand, Annas, Ekblom, Orelund, & Fredrikson, 2001). Für den Trait-Ansatz spricht auch die hohe zeitliche Stabilität von Konditionierungsmustern (Blechert, Michael, & Wilhelm, in preparation; Fredrikson, Annas, Georgiades, Hursti, & Tersman, 1993) sowie erste Evidenz, dass Konditionierbarkeit auch im Längsschnitt mit der PTSD Entwicklung vorausgeht (Guthrie & Bryant, 2006).

Im Gegensatz zur Trait-Ansätzen stehen Theorien, die erhöhte Konditionierbarkeit als ein Resultat einer Stress-Sensitivierung ansehen (State-Ansatz, Nemeroff et al., 2006; Rau, DeCola, & Fanselow, 2005). Während die meisten Befunde zur Stress-Sensitivierung aus tierexperimentellen Untersuchungen stammen, konnte kürzlich eine erste Humanstudie zeigen, dass sozialer Stress eine nachfolgende Furchtkonditionierung potenzierte (Jackson, Payne, Nadel, & Jacobs, 2006). Die Gültigkeit von Trait vs. State Ansätzen lässt sich wahrscheinlich nur in weiteren longitudinalen Untersuchungen klären.

4.5 *The big picture: Psychophysiologisches Assessment – Implikationen für Diagnostik, Genetik und Therapie*

Die beiden klinischen Studien PASS und ACP haben mittels psychophysiologischer Methoden störungsspezifische Charakteristika und veränderte Lernmechanismen der PTSD identifiziert. Im Folgenden sollen die Implikation dieser Befunde für Diagnostik (4.5.1), psychiatrische Genetik/Endophänotypen (4.5.2) und differenzielle Therapieindikation (4.5.3) diskutiert werden.

4.5.1 **Tonisches Hyperarousal: Implikationen für Diagnostik und Klassifikation**

Die PASS bestätigte frühere Befunde von kardiovaskulärer Übererregung (z.B. erhöhte HR und elektrodermales Arousal) und zeigte die zugrunde liegenden autonomen Mechanismen auf (z.B. vagale Unteraktivierung). Zudem erbrachte sie erstmals Anzeichen für respiratorische Dysregulation in dieser Patientengruppe. Ein wichtiger Befund der multivariaten Analyse war, dass 70 % der PTSD Patienten allein aufgrund ihrer psychophysiologischen Aktivierung korrekt der PTSD Gruppe zugeordnet werden konnten (Sensitivität). Umgekehrt wurden 88% der nicht-PTSD Patienten korrekt einer der anderen Gruppen zugeordnet (Spezifität). Diese hohe Assoziation physiologischer Merkmale mit diagnostischer Klassifikation ist bemerkenswert vor dem Hintergrund, dass keine störungsspezifische Stimulation stattfand. Erhöhte Reaktionen auf Traumareize wurden in eine Vielzahl von Studien für PTSD Patienten belegt. Orr und Roth (2000) fassten vier dieser Studien zusammen, indem sie die prädiktive Diskriminanzanalysen, welche die Gruppenzugehörigkeit vorhersagen, sukzessiv an den anderen Stichproben kreuzvalidierten. Die finale Diskriminanzanalyse umfasste 75 PTSD Patienten und erbrachte eine Sensitivität von 60% und eine Spezifität von 89%. Im Vergleich zu diesen Studien ist die Klassifikationsgenauigkeit der in der PASS Stichprobe erstaunlich hoch, eine Kreuzvalidierung wäre hier sicherlich wünschenswert. Allerdings ist auch denkbar, dass die methodische Qualität der Messungen und die Breite der erfassten Parameter für die Genauigkeit der Klassifikation entscheidend sind.

Die Befunde zur „psychophysiologischen Klassifikation“ machen das Paradox in der Diagnostik von PTSD Patienten deutlich: zwar hat die DSM-IV Diagnose ausdrücklich psychophysiologische Studien berücksichtigt, indem das Kriterium B5 erhöhte körperliche

Reaktionen auf Traumareize beurteilt, die Praxis der aktuellen Diagnostik beruht jedoch ausschließlich auf den Selbstbericht solcher körperlicher Reaktionen. Die psychophysiologische Messung solcher Reaktionen hat bisher noch nicht Eingang in die standardisierte Diagnostik gefunden (Wilhelm & Roth, 2001).

Konditionierbarkeit, wie in der FCP Studie untersucht, hat nicht in gleicher Weise diagnostische Implikationen wie tonisches Hyperarousal. Zum einen ist ein solches Paradigma für die diagnostischen Routineeinsatz zu aufwendig, zum anderen ist die Störungsspezifität nicht gesichert. Verzögerte Löschung wurde bereits bei PD und Sozialer Phobie, sowie bei einer gemischten Angstgruppe nachgewiesen (Hermann, Ziegler, Birbaumer, & Flor, 2002; Michael et al., submitted; Pitman & Orr, 1986). Verzögerte Löschung scheint demnach eher ein genereller prädisponierender Faktor für Angststörungen zu sein.

4.5.2 Psychophysiologische Endophänotypen

Für PD und PTSD ist mittlerweile eine moderate Heredität nachgewiesen worden (Hettema, Neale, & Kendler, 2001; Stein, Jang, Taylor, Vernon, & Livesley, 2002). Bisher ist die Suche nach angstspezifischen Genen jedoch noch nicht schlüssig und es sind z.T. sehr große Stichproben notwendig, um Zusammenhänge zwischen Genotyp und psychiatrischem Phänotyp aufzudecken (z.B. Freeman, Roca, Guggenheim, Kimbrell, & Griffin, 2005; Zhang et al., 2006). Smoller und Tsuang (1998) beschreiben verschiedene Gründe, warum die spezifischen Gene, die diesen Störungen zugrunde liegen, noch nicht identifiziert werden konnten. Demnach dienen die traditionellen psychiatrischen Kategorien vor allem der klinischen Kommunikation und der reliablen Unterscheidung von Störungen mit Hilfe interviewbasierter Diagnostik. Für die Identifikation genetischer Loci seien diese Kategorien jedoch zu breit und zu heterogen. Unter den Begriff „psychiatric genetic nosology“ schlagen sie eine auf genetische Loci abgestimmte Diagnostik vor, die „genetische Phänotypen“ identifizieren soll. Die Idee der genetischen Phänotypen wurde zum Konzept der Endophänotypen verfeinert (de Geus, 2002; Gottesman & Gould, 2003; Lenzenweger, 1999), für das mittlerweile eine Reihe von Definitionskriterien vorliegen. Lenzenwenger (1999) beschreibt Endophänotypen als „indicators of liability not visible to the unaided naked eye“. Gottesman und Gould (1993) bezeichnen Endophänotypen als „measurable components along the pathway between disease and distant genotype“.

Die klinische Psychophysiologie kann nun solche Endophänotypen definieren, in dem sie u.a. nachweist, dass ein bestimmtes physiologisches Aktivierungsmuster verlässlich mit einer psychiatrischen Störung assoziiert und state-unabhängig ist, d.h. z.B. der Störung vorausgeht.

Zudem muss für Endophänotypen (im Unterschied zu biologischen Markern) Heredität nachgewiesen sein, d.h. der Endophänotyp muss in gesunden Angehörigen oder Zwillingsgeschwistern von erkrankten Personen gehäuft auftreten. Diese Forschungsrichtung wurde kürzlich als „Genetische Psychophysiologie“ eingeführt (de Geus, 2002).

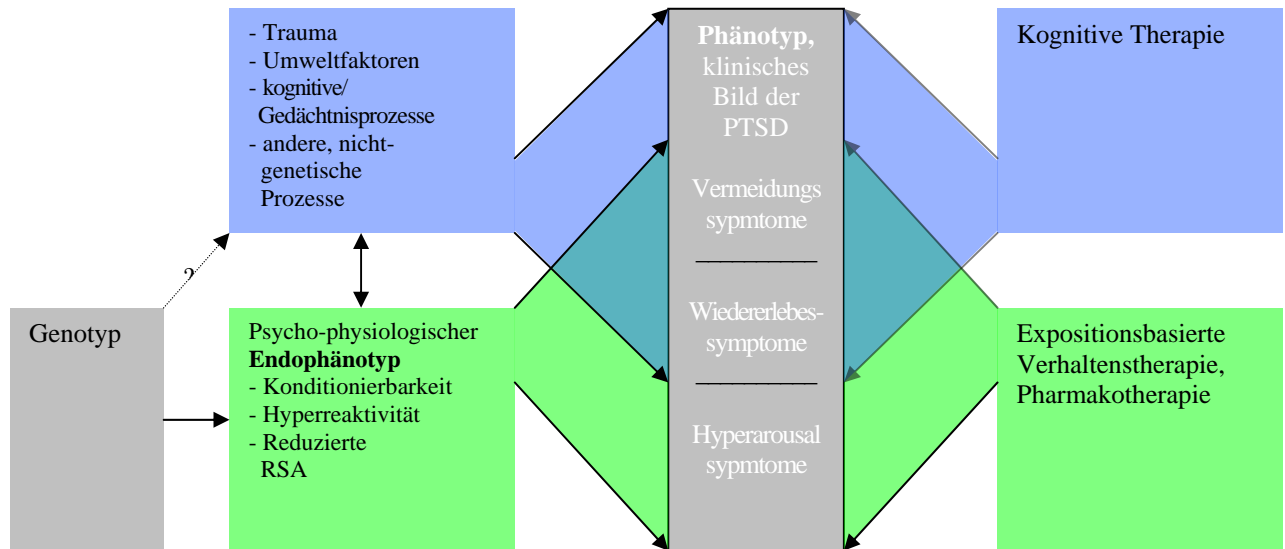
Die PASS Studie hat verschiedene physiologische Systeme identifiziert, die eine reliable und störungsspezifische Assoziation mit der PTSD Störung bzw. der PD Störung aufwiesen. Interessanterweise gibt es nun auch vermehrt Belege, dass diese Parameter (z.B. HR, RSA) zu einem großen Teil genetisch bedingt sind (z.B. Kupper et al., 2005). Mittlerweile hat die Forschung nun begonnen, psychophysiologische Endophänotypen bei gesunden Angehörigen von Panikpatienten zu untersuchen, z.B. mit CO₂-Provokationstests (Coryell, Pine, Fyer, & Klein, 2006; Pine et al., 2005). Die Befunde der PASS Studie könnten ein Ausgangspunkt sein, autonome und respiratorische Parameter bei gesunden Angehörigen von PTSD Patienten zu untersuchen.

4.5.3 Endophänotypen, biologische Marker und differenzielle Therapieindikation

Die Konzeptualisierung von Endophänotypen eröffnet eine hilfreiche Perspektive auf die Zusammenhänge zwischen Genotyp, Phänotyp und Umweltfaktoren, wie er in Graphik 4 für die PTSD Störung hypothetisch dargestellt wird. Demnach interagieren genetische- und Umweltfaktoren in der Verursachung posttraumatischer Symptomatik. Psychophysiologische Endophänotypen wie Konditionierbarkeit oder Hyperarousal nehmen dabei eine medierende Position zwischen Genotyp und Phänotyp ein und beeinflussen bestimmte Symptomcluster (Hyperarousalsymptome, Wiedererlebenssymptome) mehr als andere (Vermeidungssymptome).

Was sind jedoch die Implikationen für die Therapie? Das Rational der Expositionstherapie der PTSD geht von der Annahme abnormer Konditionierungsprozesse, insbesondere einem Defizit in der Furchthemmung aus (Rothbaum & Davis, 2003), was in der FCP Studie belegt werden konnte. Demnach ist Expositionstherapie nur für die Gruppe von PTSD Patienten indiziert, welche den Endophänotyp erhöhte Konditionierbarkeit zeigt. Dieser Endophänotyp wiederum sollte sich überwiegend in ausgeprägten Wiedererlebenssymptomen ausdrücken. In gleicher Weise sollte eine therapeutische und pharmakologische Behandlung von Hyperarousalsymptomen nur bei Patienten indiziert sein, bei denen z.B. niedriger RSA und erhöhte HR (Endophänotyp) objektiv vorliegt (siehe auch Bryant, Harvey, Guthrie, & Moulds, 2000). Diese Zusammenhänge sind in Graphik 4 (rechte Seite) dargestellt.

Graphik 4: Hypothetische Rolle von Genotyp, Endophänotyp und Umweltfaktoren für verschiedene Symptomcluster der PTSD (linke Seite). Rechts die Zusammenhänge von Therapieformen und Symptomclustern.



Anmerkung: Das vierte Symptomcluster „emotional numbing“ ist hier nicht dargestellt, da hierzu keine Hypothesen vorliegen

Es ist offensichtlich, dass ein so umfassendes Modell noch umfangreich überprüft werden müsste. Die vorliegende Arbeit stellt hier einen ersten Schritt dar, in dem neben methodischen und theoretischen Aspekten psychophysiologischer Messungen (Studien STATE, und RATE) die Rolle von psychophysiologischer Dysregulation und Furchtextinktion (Studien PASS, und RATE) bei PTSD herausgestellt wurde.

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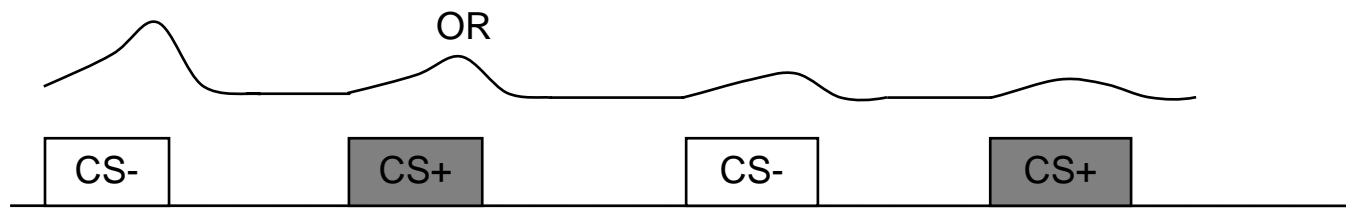
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Graphik 1. Darstellung des differentiellen Konditionierungsparadigmas: Konditionierte Stimuli, beispielhafter Verlauf der Hautleitfähigkeit, sowie Benennung ihrer Komponenten

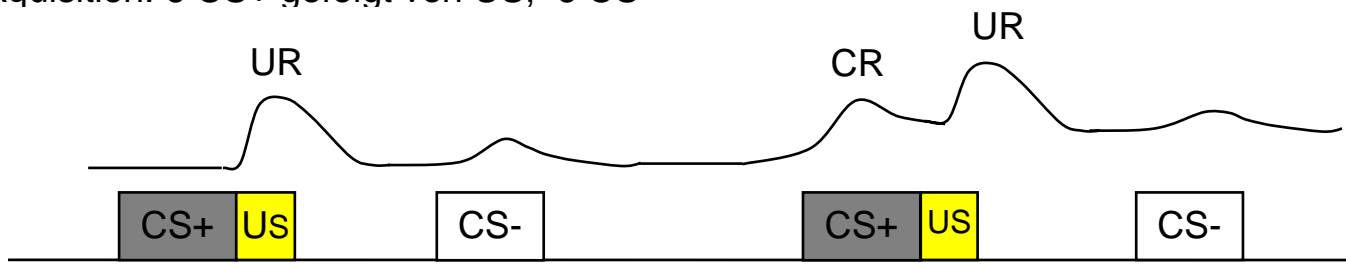
Habituation: 6 CS+, 6 CS-



CS+, CS-



Akquisition: 6 CS+ gefolgt von US, 6 CS-

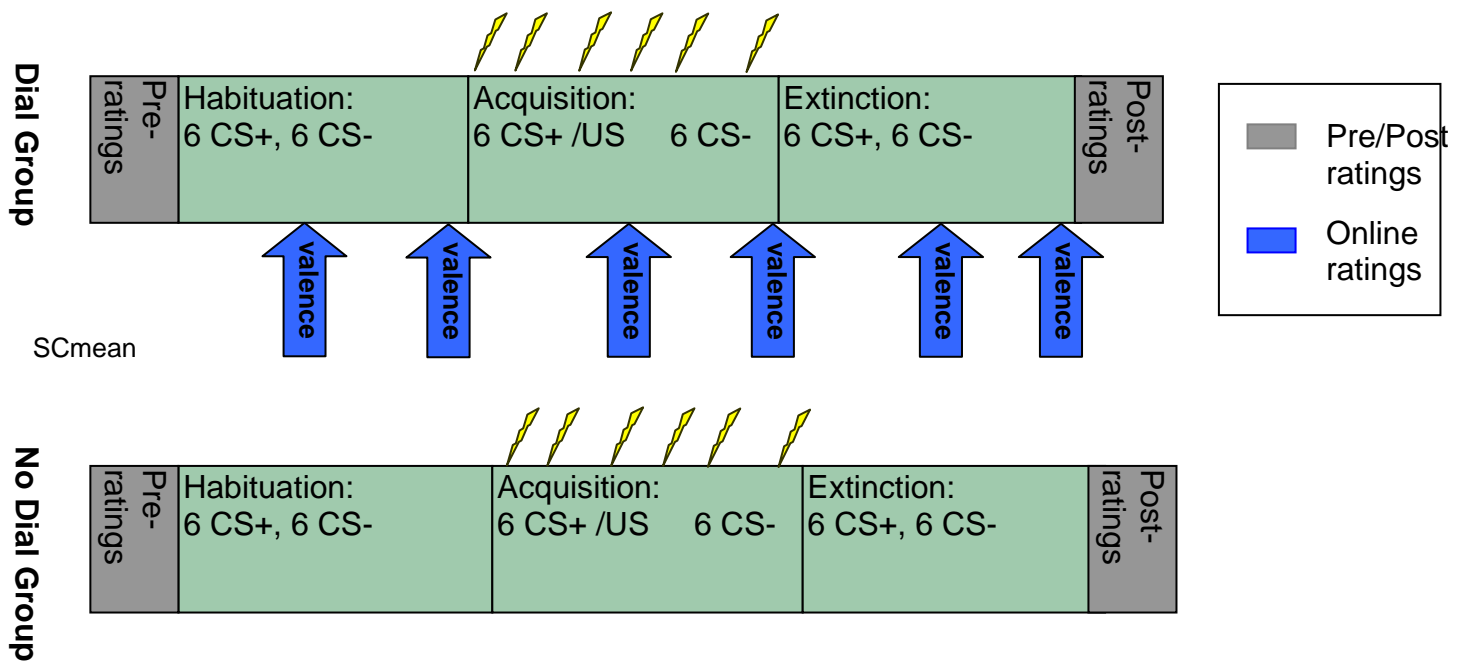


Extinktion: 6 CS+, 6 CS-



Anmerkung. CS, Conditioned Stimulus; CR, Conditioned Response; US, Unconditioned Stimulus; UR, Unconditioned Response

Graphik 2. Studiendesing von Studie RATE. Konditionierungsphasen, Ratingprozeduren und Kontrollgruppe



Anmerkung. CS, Conditioned Stimulus; US, Unconditioned Stimulus

Identifying anxiety states using broad sampling and advanced processing of peripheral physiological information

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KEYWORDS

Psychophysiology, Affective Computing, Anxiety, Emotion, Autonomic Nervous System, Respiratory Sinus Arrhythmia, Skin Conductance, Heart Rate, Respiration, Capnometry, Accelerometry

ABSTRACT

Advances in biosignal acquisition and processing have provided an effective window to the complex peripheral physiology related to human emotions. Numerous cardiovascular measures have been used for assessing the activity of the sympathetic and parasympathetic branches of the autonomic nervous system. More recently, respiratory parameters have shown promise for the assessment of anxiety. Current theoretical accounts of anxiety recommend a broad assessment of anxiety responses involving measures from the physiological, behavioral and verbal-cognitive domain. However, practical and statistical considerations put restrictions on the number of dependent variables used in studies on emotion. In a laboratory experiment we assessed a large number of psychophysiological parameters to identify their relative utility for differentiating between a neutral (quiet sitting) and an anxious state induced by threat of shock. High effect sizes were found in all psychophysiological systems with electrodermal and behavioral responses demonstrating the highest, and respiratory and cardiovascular responses yielding medium and small effect sizes. A linear combination of the six most powerful variables was highly significant in distinguishing the neutral from the anxious state and resulted in 83.3% correct classification. Results demonstrate the necessity to include measures from multiple response domains for an adequate assessment of anxiety states. Furthermore, our results point to the significance of respiratory parameters in anxiety assessment.

INTRODUCTION

Psychophysiological assessment of the psychological state of anxiety under controlled laboratory settings has broadened the understanding of emotions in healthy and in clinical populations. Lang's [1] three-systems approach to anxiety has provided both a structure and rationale for inclusion of physiological measures in anxiety assessment. He argued that anxiety manifests in three independent modes of response: verbal-cognitive, behavioral, and physiological. According to this view, adequate measurement of anxiety should involve indicators from each of the three response domains. Research in anxiety, however, has often found discordance between response modes, e.g., experience of anxiety without significant changes in physiological activation or overt behavior [2]. Consequently, the correlations of these three systems are in the order of 0.3-0.6 [1-3]. The concept of three "loosely coupled" response systems [3], creates a paradoxical situation: assessing just one system of anxiety is insufficient, assessing more than one reveals their discordance. Diagnostic systems like the DSM-IV [4] solve this problem by relying on the self-report of bodily symptoms at the cost of well known biases associated with it [2].

The problem of discordance arises not only *between*, but also *within* response modes: some anxiety provoking procedures activate electrodermal but not cardiovascular measures, and vice versa [5]. The concept of situational response specificity (SRS) is used to describe the specific psychophysiological response profile elicited by a specific situation across individuals. Besides SRS, individual response specificity (IRS), the disposition of subgroups of individuals to consistently show a certain pattern of physiological responses [6], is another source of discordance within the psychophysiological response domain.

Measurement of the complex bodily changes accompanying anxiety thus requires *broad* sampling of response systems to accommodate for IRS. Secondly, channels need to be selected and processed to ensure their *sensitivity* to the specific experimental situation (SRS).

Advances in psychophysiological recording techniques have broadened the range of available channels. However, the sensitivity of extracted parameters depends on the quality of the signal processing. The electrocardiogram (ECG), for example, not only allows for the computation of HR, but also respiratory sinus arrhythmia (RSA), an index of cardiac parasympathetic activation [7] and T-wave amplitude, an index of cardiac sympathetic activation [8]. In addition to averaging across measurement intervals, computing beat-by-beat or breath-by-breath variability has demonstrated its usefulness. For example, the root mean squared successive difference (RMSSD) of tidal volume and the tidal volume variability computed by complex demodulation (CDM) are parameters associated with clinical anxiety [9]. Thus, a single channel can provide several meaningful psychophysiological parameters, and thus the number of measures is large when several channels are recorded. However, current knowledge is incomplete as to their relative utility in indexing psychological states.

On the other hand, several methodological problems arise with the inclusion of ever more channels and dependent variables. Firstly, with multiple univariate testing, α -error probability is increasing. Secondly, different measures influence each other, e.g., the measurement of eye-blink startle – requiring the presentation of an intense auditory signal – disturbs the measurement of skin conductance response. Thirdly, some measures from complex methods like brain imaging are problematic in that they render the laboratory situation more threatening, hereby possibly interfering with the intended experimental manipulation of psychological state.

Even the most adequate measurements are blunt without an appropriate laboratory procedure to elicit the emotion of interest. Anxiety has been conceptualized as an apprehensive anticipation of future threats whereas fear is associated with a clearly identified imminent threat [10]. With fear being a rather phasic, short-term response, anxiety can be thought of as a more long-lasting tonic state [11]. A laboratory model should therefore elicit an enduring aversive state of anticipation of negative events. The threat of shock paradigm [12] seems to be a good candidate for the elicitation of the psychological state of anxiety. Instructions inform participants of inescapable future shock. No information is available about the time of the shock (unpredictability), causing a state of aversive, anxious tension. Using the threat of shock paradigm, the present study aims to identify psychophysiological channels and measures that can best index the psychological state of anxiety. The processing of these channels is being described and results regarding their discriminative power are being presented.

METHODS

Participants. Forty-two participants (14 men, 28 women) were recruited from the general population through advertisement posted on the Internet describing a study of mental stress assessment. Participants' age was 42.2 ± 9.9 (mean \pm SD). Individuals with a medical history of conditions that might affect the physiological systems under study were excluded. Participants had undergone a prior session in the laboratory related to a different research question and were thus well adapted to the laboratory.

Procedures. After the procedures were fully explained, all participants signed an informed consent form approved by the local ethics committee. Following the filling in of a number of questionnaires, all electrodes and sensors were attached. Two Ag/AgCl electrodes at the lower arm were connected to an electrical stimulator (constant current unit, Biopac Systems, Inc., Goleta, CA, USA) producing AC current

of 500 ms duration at a button press. Participants were asked to press the button repeatedly and find an electric current level acceptable for the experiment. They were asked that ideally this would be a level that was “highly unpleasant but not painful”. Then respiratory sensors were calibrated by having participants breathe in and out of an 800 ml bag 6 times, filling and emptying it completely. For the baseline phase, electrodes at the lower arm were detached and participants were instructed to sit quietly for 5 minutes and that no electrical current would be applied. For the threat of shock phase, electrodes were attached to the lower arm and participants were instructed that two pictures would appear on the screen occasionally, one of them sometimes being accompanied by an electrical current. During this 5-min phase, a total of 12 pictures appeared. However, no electrical current was being applied. After two additional experimental phases (results not presented here) all electrodes and sensors were removed and participants were paid and debriefed.

Data acquisition. Seven physiological channels were recorded using the Biopac MP150 system at a rate of 1000 Hz in a continuous mode. Two channels of respiration were measured with pneumatic bellows placed around the chest and abdomen. Electrocardiogram lead II was recorded from three standard ECG electrodes. Expiratory partial pressure of CO₂ (pCO₂) was measured continuously from air sampled at the nostrils using a calibrated infrared capnograph (Nellcor N-1000, Hayward, CA). Body movement was sensed by an accelerometer attached to the left shoulder. Skin conductance data were obtained from the index and the middle finger of the left hand and electromyographic activity (EMG) from the left facial corrugator muscle. The arterial pulse wave was assessed using a plethysmograph transducer (Nellcor N-1000) attached to the tip of the participant’s second finger.

Data reduction. Physiological signals were analyzed and averaged for each phase using an integrated suite of biosignal analysis programs written in MATLAB (Mathworks, Inc., Natick, MA) [13, 14]. Cardiovascular and respiratory channels provided a number of parameters and are thus described in more detail here. The ECG was analyzed with a program that detects R-waves and calculates consecutive RR intervals (in ms). Beat-by-beat values and T-wave amplitudes were edited for outliers due to artifacts or ectopic myocardial activity by computer algorithm and visual inspection. Respiratory sinus arrhythmia (RSA, in ms²) was quantified as lnHF power using fast Fourier transform and the Welch algorithm as the summed spectral density function within the frequency band associated with respiration (0.13-0.50 Hz)[15], by using complex demodulation [16], and by using a bandpass filtered variance technique [17]. Finger pulse wave transit time (PTT) was indexed by the time (in ms) elapsed between the closest previous R-wave and the upstroke of the peripheral pulse at the finger. Puls wave amplitude (PWA) was computed as the difference between the peak and valley of each pulse wave. Besides a number of self-explanatory respiratory timing parameters, the duty cycle was computed as inspiratory time divided by total time. Variability parameters of respiration were root mean squared successive difference (RMSSD) of breath-by-breath tidal volume and total time, and the complex demodulated amplitude of these measures [9].

Statistical analysis. As a quantification of the strength of discriminatory power for different measures during neutral and anxious states, effect sizes were calculated which are independent of sample size [18]. Effect sizes inform about differentiation of conditions expressed as difference divided by pooled standard deviations. The level of significance of differences (*p*-value) is calculated by *t*-test. In addition, absolute difference (anxious - neutral) and % difference (100 · difference/neutral) are provided to illustrate the magnitude of change from baseline. Discriminant function analyses (DFAs) were calculated for each measure separately to estimate the % correct identification of phases based on the measure (50% is chance level). In addition, a DFA was calculated for a subset of measures with the largest effect sizes.

RESULTS

Results of the statistical analysis for parameters for indexing differences between the neutral and anxious state are displayed in Table 1.

Table 1. Statistical parameters for distinguishing neutral from anxious state: Cohen's effect sizes d (0.3 is small, 0.5 is medium, 0.8 is large), level of significance (p-value), differences (absolute, %), and correct classification for all parameters.

Channels/Parameters	Effect size	P-value	Difference	Difference (%)	% Correct	Channels/Parameters	Effect size	P-value	Difference	Difference (%)	% Correct
Respiratory						Cardiovascular					
Respiratory rate ¹ (cpm)	0.78	0.00	4.66	30.71	56.3	Pulse wave ampl. (units)	-0.79	0.00	-0.94	-24.79	60.9
CDM ampl. tidal volume (ml)	0.65	0.00	52.80	110.05	60.6	RR interval (ms)	-0.32	0.09	-15.76	-4.13	61.1
Sigh frequency (1/min)	0.63	0.00	1.15	154.87	65.6	Heart rate (bpm)	0.29	0.10	1.81	6.66	54.7
Respiratory rate ² (cpm)	0.60	0.00	4.38	31.54	59.1	LF/HF-ratio for CDM ampl.	-0.24	0.17	-0.11	-34.64	64.1
RMSSD total time (s)	0.56	0.01	0.21	91.41	56.1	LF/HF-ratio for power	-0.16	0.36	-0.01	-5.34	59.4
CDM amplitude total time (s)	0.55	0.00	0.21	127.76	60.6	RSA (Porges)	0.05	0.77	0.09	15.61	56.9
Non-sigh tidal volume (ml)	-0.54	0.00	-90.44	-25.85	57.6	lnVLF power (ms ²)	0.30	0.10	0.32	5.60	50.0
RMSSD tidal volume (ml)	0.52	0.01	51.90	116.53	62.1	lnLF power (ms ²)	-0.16	0.36	-0.26	-6.64	59.7
Inspiratory time (s)	-0.51	0.01	-0.19	-18.02	59.1	lnHF power (ms ²)	0.02	0.91	0.03	6.21	50.0
Expiratory time (+ pause, s)	-0.44	0.02	-0.28	-26.52	59.1	CDM VLF amplitude (ms)	0.23	0.22	4.29	31.94	51.5
Inspiratory time (+ pause, s)	-0.44	0.03	-0.16	-16.47	57.6	CDM LF amplitude (ms)	-0.22	0.25	-3.72	-39.09	50.0
Expiratory time (s)	-0.43	0.02	-0.20	-25.08	56.1	CDM HF amplitude (ms)	0.04	0.85	0.48	52.57	50.0
Tidal volume (ml)	-0.42	0.02	-72.18	-26.47	56.1	T-wave amplitude (mV)	-0.01	0.96	-0.00	-23.88	50.0
PCO ₂ (mm Hg)	-0.33	0.08	-0.42	-2.67	54.7	Pulse transit time (s)	-0.00	0.98	-0.07	-3.17	50.0
Duty cycle (ratio)	0.30	0.09	0.01	8.55	57.6	Electrodermal					
Expiratory pause (s)	-0.27	0.16	-0.07	-49.15	56.1	NS-SCR rate (1/min)	1.46	0.00	8.35	580.0	74.2
Inspiratory pause (s)	-0.20	0.27	-0.00	-23.36	57.6	SCR amplitude (μS)	0.98	0.00	0.16	147.65	72.6
Minute ventilation (l/min)	0.19	0.29	0.30	14.40	51.1	SCL (μS)	0.86	0.00	0.97	16.97	59.7
Sigh tidal volume (ml)	0.12	0.69	32.30	251.92	59.5	Behavioral					
% thoracic tidal volume	-0.11	0.53	-0.01	-5.83	53.8	Accelerometry (g)	1.22	0.00	0.03	53.81	51.5
Inspiratory flow rate (ml/s)	0.06	0.74	4.63	16.63	50.0	EMG corrugator (units)	0.95	0.00	0.04	55.49	51.5

Note: ¹from capnometry; ²from pneumatic bellows; VLF = very low frequency (025-.07 Hz); LF = low frequency (.07-.13 Hz); HF = high frequency (.13-.50 Hz); CDM = complex demodulation; NS-SCR = non-specific skin conductance reactions; SCL = skin conductance level

Six variables with high effect sizes representing different physiological systems or concepts (respiratory rate, CDM amplitude of tidal volume, pulse wave amplitude, RR interval, NS-SCR rate, and accelerometry) were entered into a multivariate DFA. The analysis yielded a highly significant solution, Wilks' $\lambda = .499$, $\chi^2 = 38.18$, $df=6$, $p>.000$, with 83.3% correctly classified conditions.

DISCUSSION

This study examined the relative potency of psychophysiological measures for differentiating between an anxious and non-anxious state. A large number of respiratory parameters and some parameters from other channels significantly differentiated anxiety from a neutral state (see column "p-value" in Table 1). Electrodermal and behavioral parameters provided the highest absolute effect sizes. On the other hand, many parameters did not provide much information regarding the emotion condition in which they were measured.

With respect to the respiratory domain, respiratory rate yielded the highest absolute effect size of about 0.8, with about 30% acceleration of breathing during the anxiety phase. But also variability parameters of respiration demonstrated discriminative power: both breath-by-breath variability in tidal volume and total time had medium to large effect sizes. The specific method of calculating them (using the RMSSD statistic or complex demodulation) did not seem to matter much. Our results indicate that frequent sighing, found especially in panic disorder during baseline assessment [19], appears to play a role in anxiety states in healthy participants as well: sighing is increased by over 150% during anxiety.

The highest effect size within the cardiovascular domain was found for pulse wave amplitude. This indicates considerable sympathetically mediated vasoconstriction in the anxious state. Surprisingly, however, the two other cardiovascular sympathetic parameters, namely pulse transit time and T-wave amplitude, did not show any effect. It appears that the threat of shock paradigm specifically caused the peripheral vasculature to constrict, hinting at an evolutionarily evolved defense mechanism preventing blood loss in the event of a strike. Effect sizes for the different measures of heart rate variability, including measures of RSA, were small with no clear advantage for complex demodulation vs. spectral analysis derived indices. However, other studies of more intense anxiety provokations have demonstrated the sensitivity of these measures to anxiety [e.g., 20]. One can speculate that these indices react only above a certain threshold of anxiety stimulation, exhibiting a nonlinear relationship.

The largest effect sizes were observed in the electrodermal system. This may indicate that this channel is particularly useful in anxiety assessment, as has been shown previously [21]. However, one limitation of the current study is that during the threat of shock phase – but not during the baseline – pictures were shown repeatedly. Thus, the two conditions were not strictly parallel with respect to parameters measuring phasic reactivity like SCR amplitude or NS-SCR rate. Nevertheless, in the anxiety condition SCL, a tonic electrodermal measure, was elevated by 0.86 μS which is consistent with existing research [20, 22].

With respect to behavioral data, both physical activity as well as corrugator muscle activity were elevated during anxiety. While short phasic responses of the corrugator muscle have been found in participants viewing unpleasant pictures or listening to unpleasant words or sounds [23], presentation of pictures in the threat of shock condition was brief, and pictures were of neutral valence. Thus, it is likely that participants activated this muscle in a tonic manner throughout the measurement period.

When variables are considered individually, the low percentages of correct classifications into anxious vs. nonanxious conditions are unsatisfactory: 50% (chance level) to 74% (NS-SCR rate). This inability of single measures to differentiate between neutral and anxious states for all participants is an indication of the IRS discussed above. When combining the strongest measures from each domain, however, the classification can be clearly improved.

CONCLUSIONS

While theoretical accounts of anxiety and findings of IRS urge researchers to acquire a broad set of channels, statistical and practical considerations suggest a limitation on a subset of variables. Our results indicate that measurement of anxiety across different physiological systems and aggregation of response scores may be a good compromise.

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AUTONOMIC AND RESPIRATORY CHARACTERISTICS OF POSTTRAUMATIC STRESS DISORDER AND PANIC DISORDER

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Running title: Autonomic and respiratory characteristics

Abstract

Objective: Posttraumatic stress disorder (PTSD) and panic disorder (PD) are two anxiety disorders with substantial diagnostic overlap, but also differences in their symptom profile. The PTSD criterion of persistent hyperarousal suggests autonomic dysregulation and the disorder has been associated with elevated heart rate. In contrast, PD has been associated with respiratory abnormalities such as low end-tidal pCO₂. An integrated and detailed analysis of autonomic and respiratory function in a direct comparison of these anxiety disorders is currently lacking. **Methods:** Twenty-four PTSD patients, 26 PD patients, and 35 healthy individuals were examined at rest for electrodermal, cardiovascular, and respiratory psychophysiology measures. **Results:** PTSD patients were characterized by attenuated respiratory sinus arrhythmia (RSA, a measure of cardiac vagal control), even when adjusting for respiratory and other confounds. In addition, they displayed elevated heart rate and high electrodermal and cardiovascular sympathetic arousal in comparison to the other groups. Compared to healthy controls, PD patients exhibited lower pCO₂ (hypocapnia) and higher cardiovascular sympathetic activation. PTSD patients, but not PD patients, sighed more frequently than controls. Multivariate diagnostic classification accuracy based on these measures was 64.7%. **Conclusions:** Tonic hyperarousal symptoms in PTSD are likely due to high sympathetic activity coupled with low parasympathetic cardiac control. Subtle respiratory abnormalities were also present in PTSD. Several peripheral psychophysiology measures exhibited group comparison effect sizes in the order of 1.0, supporting their potential for enhancing differential diagnosis and for being utilized as endophenotypes in molecular genetic studies of anxiety disorders.

Acronyms:

CSI=cardiovascular sympathetic index

ESI=electrodermal sympathetic index

HR=heart rate

HP=heart period

RSA=respiratory sinus arrhythmia

NS-SCR=number of non-specific skin conductance fluctuations

HRV=heart rate variability

SCL =skin conductance level

pCO₂=end-tidal partial pressure of CO₂

PDS=Posttraumatic Diagnostic Scale

PTSD=posttraumatic stress disorder

PD=panic disorder

PNS=parasympathetic nervous system

SSRIs=selective serotonin reuptake inhibitors

SNRIs=selective noradrenalin reuptake inhibitors

STAI=State-Trait Anxiety Inventory

BDI=Beck Depression Inventory

ASI=Anxiety Sensitivity Index

MI=Mobility Inventory

SCR_{amp}=magnitude of non-specific skin conductance responses

ECG=electrocardiogram

lnLF=low frequency power of HP variability

lnVLF=very low frequency power of HP variability

MANOVA=multivariate analyses of variance

HC=healthy controls

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1) physical symptoms play a role in the diagnosis of almost all anxiety disorders. In posttraumatic stress disorder (PTSD) and panic disorder (PD) physical symptoms can become a central concern for patients. PD and PTSD exhibit a partial diagnostic overlap and frequently co-occur (2) but may differ in their underlying physiology. Persistent *tonic* hyperarousal symptoms, such as hypervigilance, sleep disturbance, and exaggerated startle response, are characteristic for PTSD. In contrast, PD patients experience recurrent *phasic* panic attacks characterized by a range of physical symptoms, among which cardiac (palpitations, racing heart) and respiratory symptoms (shortness of breath, feelings of suffocation) figure prominently. Thus, despite possible diagnostic overlap between these anxiety disorders their symptom profile suggests a different underlying physiology.

From a clinical point of view the elucidation of specific psychophysiological signatures of these disorders could aid a differential diagnosis by complementing diagnostic interviews (3). Similarly, although convincing evidence of heritability of these disorders has been presented (4, 5), their precise genetic basis has yet to be elucidated. To this end, the identification of psychophysiological endophenotypes specific to each of these disorders may facilitate research in behavior genetics of these disorders (6, 7). An endophenotype can be seen as a measurable component along the pathway between the phenotypic behavioral expression of a disorder and its genetic basis.

However, the research literature on psychophysiological functioning in PD and PTSD has yielded numerous inconsistencies (3). One reason for this might be the focus of most studies on a small number of physiological measures. This approach does not account for the complexity of interactions, for example, between sympathetic and parasympathetic branches of the autonomic nervous system or autonomic relations to the respiratory system. There is evidence (reviewed below) that these particular systems may be dysregulated in PD and PTSD. A comprehensive assessment of multiple systems and their relationships thus promises to provide a more complete picture of these disorders.

The majority of previous psychophysiological studies have used disorder-specific experimental stimuli, e.g., confrontation with trauma-scripts in PTSD or the administration of panic-provoking agents in PD. However, an integrated study of these two disorders aiming at the identification of disorder-specific endophenotypes would have to ensure that the experimental protocol is equally activating for both groups. Since PD and PTSD patients respond to different stimuli (i.e. trauma-related vs. panic-related) the condition with greatest commonality may be quiet sitting. Therefore, we have chosen baseline resting as the condition of interest in the present investigation and review evidence regarding cardiovascular, respiratory, and electrodermal measures that have been associated with PTSD and/or PD at rest.

With respect to the cardiovascular system, elevated resting heart rate (HR) represents a relatively reliable finding in PTSD (8), while in PD results are more inconsistent (9). Research recently turned to specific cardiac autonomic indices regulating resting HR: the recognition that HR is primarily under parasympathetic control during most conditions of daily life, and especially during resting phases (10), has

stimulated the assessment of heart rate variability measures, especially respiratory sinus arrhythmia (RSA). RSA is characterized by the rhythmic oscillation of HR related to phase of breathing and is associated with vagal efferent effects upon the heart. Consequently, it is often used as a non-invasive index of parasympathetic control of heart rate (11).

Sahar et al. (12) found no differences between a PTSD group and a healthy control group at rest, whereas Cohen et al. (13) found lowered resting RSA in PTSD. In a direct comparison of PTSD and PD patients with healthy controls, a second study by Cohen et al. (14) found heightened resting HR and attenuated RSA in both patient groups. Friedman and Thayer (9) reviewed a number of studies showing reduced RSA in various anxiety disorders. However, a number of carefully controlled investigations found comparable resting RSA values in PD patients and healthy controls (15-18). None of these studies has assessed sympathetic indicators.

Due to the sympathetic innervation of the electrodermal system (19), its assessment of activity has a strong tradition in peripheral psychophysiology. Elevated electrodermal baseline levels and heightened responses have been reported more frequently in PTSD patients than in PD patients (20-23) making the electrodermal system a promising candidate for psychophysiological differentiation in our study.

The respiratory system has long played a hypothetical etiological role in PD. Both the suffocation false alarm theory (24) and the hyperventilation theory (25) argue that respiratory dysregulation is a core feature of PD. A number of studies have found evidence for respiratory irregularities, such as frequent sighing (26-28) or lowered end-tidal pCO₂ in PD (18, 26, 29-31). In PTSD, a few reports have identified respiratory abnormalities during sleep (e.g. 32). However, most laboratory investigations only

measured respiration rates and did not find differences between PTSD patients and controls (e.g. 12).

In summary, evidence for sympathetic, parasympathetic, and respiratory abnormalities in PD and PTSD exists, but it is largely based on research focused on only one system at a time and only in a single disorder. The current study was designed to delineate psychophysiological differences between PTSD and PD patients and healthy control participants by examining a variety of measures of cardiovascular, electrodermal, and respiratory functioning during a standardized resting task. To account for the complexity of cardio-respiratory interrelations, special care was given to the estimation of RSA by cautiously considering potential confounders such as respiratory parameters (33) and participant characteristics. In addition, many previous experimental investigations might have failed to provide subjects with sufficient time to adapt to the laboratory situation. However, incomplete adaptation of anxiety patients could account for differences between patients and controls in baseline physiological parameters. Therefore, we assessed basal activity at the last of three visits to our laboratory. Based on previous findings we expected to find (1) elevated HR and lowered RSA in PTSD patients, (2) lowered pCO₂ and increased sigh frequency in PD patients, and (3) heightened electrodermal and cardiovascular activation in both patient groups in comparison to healthy controls. A variety of other measures were included in this investigation for exploratory purposes.

Method

Participants

The experimental groups consisted of 24 PTSD patients, 26 PD patients (with or without agoraphobia), and 35 healthy individuals who had never qualified for a psychiatric disorder and who were matched to the patient groups on age, gender, education, and smoking. The diagnosis was assessed by clinical psychologists trained in using the F-DIPS ('Diagnostic Interview for Mental Disorders – Research Revision'; (34)), a well-validated structured interview for diagnosing DSM-IV disorders. It is a modified German version of the Anxiety Disorder Interview Schedule for DSM-IV – Lifetime version (ADIS-IV-L; (35)). Trauma types in the PTSD group were accidents (traffic and work-related; n=8), physical or sexual violence (7), war-related trauma (imprisonment, torture; 3), natural disasters (2), and other traumata (4). The average duration of the PTSD diagnosis was 5.8 years (SD=8.8, range=2 months to 27 years). The following secondary disorders were diagnosed in the PTSD/PD groups: agoraphobia (1/22), major depression (8/4), social phobia (3/3), pain disorder (3/0), generalized anxiety disorder (3/4), other disorders (2/3). None of the PTSD patients had a diagnosis of PD and vice versa.

Exclusion criteria for all participants were: lifetime history of psychosis, bipolar disorder, drug abuse or dependence, a medical history of conditions that might affect the physiological systems under study (e.g., angina, myocardial infarction, asthma), and the use of medication with strong autonomic effects such as benzodiazepines, β -blockers, sympathomimetic drugs, antipsychotics, or tricyclic antidepressants. Of the included PTSD/PD patients, 7/4 took analgesic drugs and 1/4 took selective serotonin or

noradrenalin reuptake inhibitors. Participants were told to abstain from alcohol or recreational drugs for 24 hours before testing. They were either referred to us by collaborating mental health institutions or responded to advertisements in the local media.

Psychometric assessment of the study groups included the German versions of the State-Trait Anxiety Inventory, STAI (36); the Beck Depression Inventory, BDI (37); the Anxiety Sensitivity Index, ASI (38); and the Mobility Inventory, MI (39). Only the PTSD patients completed the Posttraumatic Diagnostic Scale, PDS (40), since the questions refer to the traumatic event. The study was approved by the local ethics committee for medical research and participants gave written consent before participating. Each participant received a reimbursement of 90 CHF (approximately 70 USD).

Procedure

The diagnostic status of the participants was determined in an initial session, which was followed by two independent experimental sessions one week apart. The assessment of psychophysiological measures was always scheduled to the second experimental session, in order to facilitate the adaptation to the laboratory environment and the experimenters. On study entry participants had agreed to participate in an aversive conditioning procedure, which was conducted subsequently to the quiet sitting procedure described in the present paper and will be reported elsewhere.

The procedure took place in a temperature and sound-controlled 4 m X 2.5 m room, which was electronically connected to an adjoining room where the experimental apparatus was located. On arrival, participants were seated in upright position in a

comfortable armchair and all physiological electrodes were attached to allow adaptation to the skin and minimize measurement drifts. For the following 20 min participants completed psychometric questionnaires as well as a reaction time task which was unrelated to the present investigation. After a calibration procedure for the respiration belts, instructions appeared on the screen asking participants to sit quietly for 5 minutes with their eyes open and to not move much.

Physiological measures

Placement of electrodes/sensors, data recording, and data reduction followed conventions established for psychophysiological research and published guidelines. Physiological channels were A/D converted, sampled at 400 Hz, and simultaneously streamed to disk and displayed on a PC monitor using the Biopac MP150 system (Biopac Systems, Inc., Goleta, CA, USA). Physiological signals were analyzed and averaged for the 5-min quiet sitting period using an integrated suite of biosignal analysis programs (41). All channels were manually edited to reject movement or electronic artefacts, or ectopic beats in the electrocardiogram.

Electrodermal measures. Three parameters were calculated from electrodermal activity recorded from the middle phalanx of the index and middle finger of the left hand: skin conductance level (SCL), number of non-specific skin conductance fluctuations (NS-SCR, number of deflections from a zero-slope baseline exceeding 0.02 μ Siemens), and SCR_{amp} (magnitude of NS-SCRs).

Cardiovascular measures. From the electrocardiogram lead-II, heart period (HP) was calculated as the interval in milliseconds between successive R-waves. For statistical and physiological reasons, HP was used in all analyses (42), but for ease of

interpretation, HP was converted to HR. High frequency (lnHF or RSA), low frequency (lnLF), and very low frequency (lnVLF) powers of HP variability were computed as the natural logarithms of the summed power spectral density between 0.15-0.4 Hz, 0.05-0.15 Hz, and 0.0033-0.05 Hz respectively (see also (43)). We also calculated a HP-normalized index of RSA (Hayano index, or RSA_{norm}) which has been shown to reflect vagal control independent of sympathetic influences (44-46).

Three putatively sympathetic indicators were calculated beat-by-beat from the ECG and the finger pulse waveform (measured by a plethysmographic sensor, Nelcor N-1000, Hayward, CA, USA): T-wave amplitude, calculated in reference to the isoelectric ECG baseline (47); pulse wave transit time, as time between steepest upstroke and ECG R-wave (48, 49), and pulse wave amplitude, as peak minus trough (47, 49, 50). In order to obtain more representative and reliable indices of sympathetic cardiovascular and electrodermal activation, as well as to reduce the number of statistical tests, T-wave amplitude, pulse wave transit time and pulse wave amplitude were combined by means of z-transformation (between individuals) and averaging (within individuals) to form an cardiovascular sympathetic index, CSI. The CSI was scored inversely since the three measures are inversely related to sympathetic activation. SCL, NS-SCRs and SCR_{amp} were combined in the same way to form an electrodermal sympathetic index (ESI).

Respiratory measures. The following respiratory variables were calculated from thoracic and abdominal pneumographic respiration channels (James Long, Inc., NY) calibrated for each individual as previously described (23): respiratory rate, tidal volume, minute volume, duty cycle (inspiratory/total cycle time), sigh frequency, inspiratory flow rate, and ribcage contribution to tidal volume. Variability of respiratory cycle duration and tidal volume was assessed using complex demodulation in the frequency band 0.004–

0.14 Hz (corresponding to period lengths of 6.6–240 sec) using a transition band width of 0.033 Hz (23, 51). Expiratory pCO₂ was measured continuously using a calibrated infrared capnograph (N-1000, Nellcor, Hayward, CA) and a dual nostril prong. End-tidal values, which are close to arterial values, were scored only for breaths with a distinct plateau (see 23). All physiological data were averaged across the 5-min quiet sitting period. Physiological data were then reviewed by a senior psychophysicologist (FHW) blind to diagnostic group assignment.

Statistical analyses

A subset of primary variables directly relating to the hypotheses were selected *a-priori* (HR, RSA, CSI, ESI, pCO₂, and sigh frequency), and the remaining measures were examined for exploratory purposes. A multivariate analysis of variance (MANOVA) using primary variables was followed by ANOVAS for individual variables. When significant, pairwise Tukey post-hoc tests were performed. For the MANOVA and the calculation of correlations, sigh frequency was transformed using the natural logarithm to reduce skewness. Untransformed values were submitted to Kruskal-Wallis ANOVA by ranks followed by pair-wise Mann-Whitney-U tests. To reduce the probability of Type I errors due to multiple testing alpha level was set to .05 for primary measures and .01 for exploratory measures. Effect sizes (Cohen's *d*) were calculated for the three pairwise group comparisons. Analysis of covariance (ANCOVA) was used to assess potential covariates to group effects on RSA, since two recent reviews highlight the importance of adjusting for respiratory rate, tidal volume, and pCO₂ in the estimation of RSA (33, 46). A predictive discriminant analysis was computed to determine the extent to which cases could be accurately assigned to their respective groups based on their scores on

primary measures. Multiple regression analysis was used to examine possible respiratory determinants of pCO₂ (see 18).

Results

Subject characteristics and psychometrics. The three study groups did not differ on percentages of female participants (PTSD: 66.7%, PD: 76.9%, HC: 71.4%, respectively, $\chi^2(2, 85)=.65, p=.72$) or percentage of smokers (33.3%, 26.9%, 33.3%, 5% not answering this item, $\chi^2(2, 80)=.34, p=.85$). Table 1 shows demographic and psychometric measures for the three groups. Groups did not differ in age or years of education. In accordance with the diagnostic categorization, the patient groups scored higher than the control group on all clinical questionnaires. Interestingly, PTSD and PD patients had comparable levels on the ASI and the MI. Importantly, state and trait anxiety were similar between patient groups, but PTSD patients had higher BDI scores compared to the other groups.

Analyses of primary measures. With the use of Wilks' criterion, the MANOVA comparing the combined primary measures across the three study groups was highly significant, $F(12,140)=4.01, p<.001, \text{partial } \eta^2=.26$. Table 2 provides results of univariate analyses. Groups differed significantly on all primary measures. Post-hoc tests indicated that PTSD patients had higher ESI and lower RSA scores compared to both comparison groups. PTSD patients also showed elevated HR (attenuated HP) and sighed more frequently compared to healthy controls. PD patients had lower pCO₂ compared to healthy controls. Both patient groups demonstrated higher cardiovascular sympathetic activity as indicated by the CSI compared to controls.

Adjustments of RSA. Research has demonstrated that RSA is affected by a multitude of factors (for an overview, see 46), including respiration rate and depth, end-tidal pCO₂ (e.g. 33, 52, 53), age, and gender (54, 55). We attempted to control for the influences of these variables using ANCOVA. Respiratory rate, tidal volume, and pCO₂

were entered in the RSA analyses as covariates, both individually and in combination. All four ANCOVAs yielded significant results for the group factor, $F_s > 3.87$, $p_s < .026$, with RSA still lower in the PTSD than in other groups. The same held true when RSA was normalized for HP, $F(2,74) = 3.42$, $p = .038$, as suggested by Hayano et al. (45).

Analyses of secondary measures. Of the secondary measures, only ribcage contribution to tidal volume passed the .01 significance criterion, with PTSD patients showing less thoracic and more abdominal breathing than the other groups.

Diagnostic separation. Figure 1 displays effect sizes for the three pairwise group contrasts for primary measures. ESI and HP clearly dominate in the group contrast for PTSD vs. HC. CSI and pCO₂ primarily distinguished PD and the HC group. Importantly, the two patients groups were discriminated by ESI and RSA measures. The predictive discriminant analysis yielded an overall correct classification in 64.7% of cases. Sensitivity was lowest for the PD group compared to PTSD and HC groups (42.3%, 70.8%, 77.1%, respectively). Specificity was similar for PTSD and PD groups and lowest in the HC group (86.9%, 88.1%, 70.0%).

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Determinants of pCO₂. To explore potential sources of lowered pCO₂ in PD patients, a multiple regression analysis employed tidal volume, respiratory rate, sigh rate and minute ventilation to predict pCO₂ in the whole sample (see also 18). The model did not reach significance, $F(4,73) = 1.15$, $p = .34$. The combined predictors explained only 6% of the variance of pCO₂.

Discussion

This is the first study to provide an integrated analysis of sympathetic, parasympathetic, and respiratory psychophysiology in PTSD and PD patients. The pattern of results indicates that PTSD and PD patients were characterized by specific autonomic and respiratory abnormalities. Importantly, patient groups did not differ on state anxiety, which is a prerequisite for assigning differences between the clinical groups to their diagnosis rather than to state anxiety present in the laboratory.

Autonomic dysregulation

RSA was attenuated and HR was elevated in PTSD patients compared to healthy controls. This is in line with our expectations and previous research (8, 13). While Sahar et al (12) did not find lower baseline RSA in PTSD patients compared to controls, they only studied male patients and had a small sample size. Consistent with previous studies (20-22), PTSD patients showed elevated electrodermal and cardiovascular sympathetic arousal in comparison to healthy controls. Importantly, elevated electrodermal arousal and attenuated RSA was specific to the PTSD group: Despite similar state anxiety, PD patients did not show these features. These results suggest altered activity of both the parasympathetic and the sympathetic branch of the autonomic nervous system in PTSD, together producing the well-recognized diagnostic feature of tonic hyperarousal.

In contrast, PD patients showed more subtle autonomic dysregulation: they evidenced elevated cardiovascular sympathetic activity in comparison to controls. Yet, in agreement with at least three previous studies (15-18), no differences between PD patients and healthy controls on RSA or HR were found. This lack of strong autonomic

resting baseline findings is consistent with the clinical picture of PD, which implies phasic surges of autonomic activity during acute anxiety episodes rather than tonic hyperarousal. Instead, current theory and evidence suggests dysregulation of the respiratory system in PD.

Respiratory dysregulation

Hypocapnia (lowered end-tidal pCO₂) was the only specific marker for the PD group. This expected result is in accord with a number of previous findings of hypocapnia in PD (18, 26, 29-31). However, contrary to our expectations, PD patients did not sigh more frequently than controls, but PTSD patients did. A previous study assessed respiration during 30 min of quiet sitting in PD and found elevated sigh frequency in PD patients in comparison to controls (26). It is possible that PD patients only display elevated sigh rate after a long quiet sitting period. This would explain why we did not find this difference in the current study. Alternatively, differences in time permitted for adaptation to the laboratory context might explain these discrepant findings. In the current study, anxiety patients were well adapted to the novel and potentially frightening environment as a result of two previous visits to the lab.

Clinical lore presumes an “unhealthy” breathing pattern in anxious patients consisting of tense breathing predominantly with the chest and prescribes respiratory training to increase abdominal breathing (56). However, evidence for this breathing pattern is sparse (57). In fact, our current results indicate that PTSD patients evidenced more abdominal breathing than healthy controls. This result certainly requires replication but it highlights the weak empirical basis for an often-used clinical intervention.

Theoretical implications

Two theories emphasize a respiratory abnormality in PD patients: the hyperventilation theory (25) and the suffocation false alarm theory (24). The hypocapnia of about 3 mmHg found in our PD patients is consistent with both theories. However, the lack of group differences in pulmonary mechanics associated with hyperventilation (i.e. respiration rate, tidal volume, minute ventilation, or sighing) and a lack of predictive value of these factors for explaining low pCO₂ in a regression analysis indicates that this abnormality is due to chronic subtle hyperventilation that cannot easily be picked up by surface pulmonary sensors.

Perhaps the most notable finding of the current study is that basal autonomic functioning in PTSD but not PD is characterized by attenuated RSA. Different conceptualizations have been proposed to explain the functional biological significance of RSA and vagal activity in relationship to broad classes of behavior and higher-order processes (58, 59). RSA can reflect variations in cardiac vagal tone, phasic vagal influence upon heart rate, peripheral sympathetic-parasympathetic interactions and/or respiratory variations (46). Therefore, we carefully considered these issues in our research design and methods and also controlled for subject characteristics which could influence RSA. Our findings suggest that respiratory variations did not account for RSA differences between groups, and elevated HR confirmed cardiac autonomic effects upon PTSD patients. It remains to be explored whether RSA decrements among these patients represent primary vagal withdrawal or some secondary consequence of interactions between the two branches of the autonomic nervous system. The elevated cardiovascular and skin sympathetic responses among PTSD patients may actually suggest the latter. Nevertheless, in virtually all theoretical conceptions of RSA, basal

levels of the phenomenon represent the functional reserve capacity of the cardiorespiratory system to respond to the entire range of behavioral and metabolic requirements of the organism during normal daily activities. Lowered RSA in PTSD patients could therefore reflect decreased flexibility in adjusting to the emotional, psychosocial, behavioral and metabolic demands of everyday life, all of which could contribute to the accentuated avoidance behavior in these patients. Moreover, attenuated RSA has been found to predict cardiovascular mortality in large scale, longitudinal studies (60). Thus, the present findings may suggest important health implications for individuals suffering from PTSD.

Psychophysiological assessment: implication for diagnosis

Based on scores on the primary psychophysiological measures group, membership was correctly predicted for about two thirds of study participants, which is twice the level expected by chance. This classification accuracy is relatively high compared to other studies, even those using symptom-provocation paradigms (61). This is likely due to the comprehensive assessment of relevant physiological systems in the present study and emphasizes the value of such a broad approach. The results of the current study support the possibility that in the future, psychophysiological assessment might aid the differential diagnosis of PTSD and PD as an adjunct to diagnostic interviews. Substantial overlap in reported symptoms between PD and PTSD can cause misclassification (3) and an additional source of diagnostic information may be desirable. A 5-min resting baseline measurement would not impose much burden on patients but potentially provide relevant information.

Substantial research effort is aimed at identifying physiological diagnostic markers for mental disorders with an increasing focus on central nervous system measurement. However, the accuracy of classifications based on physiological measurement rarely exceeds 80%, even with the use of multiple electrophysiological endophenotypes in a highly heritable disorder such as schizophrenia (62). Our current analysis suggests that autonomic and respiratory functioning should not be neglected in the search for biomarkers of mental disorders since they are clearly linked to the emotion dysregulation that is common in mental disorders. It also suggests that only a combination of measures from different functional systems are likely to succeed. Unfortunately, the current study did not obtain reflexive eye-blink startle magnitude, since we thought that this may interfere with the assessment of basal physiology. However, this measure would be a good candidate to further enhance classification accuracy for PTSD (61).

Psychophysiological assessment: implication for genetic studies

Despite findings of considerable heritability in PD and PTSD (4, 5) the specific cluster of genes constituting a biological vulnerability for these disorder remains to be located (6). The present study identified several psychophysiological parameters that showed reliable and specific associations to PD and PTSD. In addition to an association with a specific disorder, a putative endophenotype has to fulfill several additional criteria (6, 7): (1) reliability and stability over time, (2) heritability, (3) state-independence, and (4) greater prevalence among healthy family members of the patient than in the general population (genetic correlation). The current results suggest several new candidate endophenotypes for further scientific study. Regarding electrodermal arousal, resting HR and RSA, both stability and heritability have been demonstrated (54, 63-66), albeit not

directly related to anxiety disorders. More research is obviously required to determine whether results of the current study pertain to real endophenotypes of PD and PTSD. One important question to be addressed is if the psychophysiological markers reflect a biological pre-disease vulnerability, which may be answered by molecular genetic studies or population-based, longitudinal research.

Limitations and conclusions

This study has several limitations. First, although we excluded any medication with direct autonomic effects, we do not know how medications (mainly SSRIs and analgesics) admitted into the study may have affected results. Second, we did not assess pre-ejection period as a measure of sympathetic cardiac modulation but instead composed an index of cardiovascular measures. However, our main conclusions do not rely heavily on this measure. Subsequent studies should assess pre-ejection period as well. Third, it is possible that differences in cardiovascular measures were mediated by subtle but significant differences between groups in physical activity during resting (i.e. PTSD patients were merely more restless than the other groups). E.g., Grossman et al (10) showed that even minor increases in metabolic activity could have an impact on RSA. Future research should address this issue. Fourth, our subjects were well adapted to the laboratory and the experimenter. Nevertheless, they were awaiting an aversive conditioning procedure, which may have elicited anticipatory anxiety. However, similarly elevated state anxiety scores in both patient groups suggest that this anticipatory anxiety affected both anxious groups to the same degree.

To conclude, this study clearly supports the idea of autonomic dysregulation in PTSD and represents the first demonstration of increased sighing in this group.

Hypocapnia was again found in PD patients. These specific autonomic and respiratory markers should be evaluated as endophenotypes in genetic studies which aim to decipher the genetic and molecular basis of PD and PTSD. Likewise, these psychophysiological signatures could assist the differential diagnosis of these two anxiety disorders.

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Table 1. Demographic and psychometric values for the study groups.

	PTSD group	PD group	HC group	F-value	Post-Hoc
	M±SD	M±SD	M±SD		
Age (years)	41.78±11.3	39.4±10.7	42.1±8.47	F(2, 81)=0.60, p=.550	
Education (years)	10.95±2.13	10.2±2.23	11.1±2.04	F(2, 79)=1.36, p=.264	
PDS	30.9±10.6				
STAI-State	50.14±7.99	48.2±11.5	37.0±8.56	F(2, 79)=16.8, p<.01	PTSD=PD>HC
STAI-Trait	55.65±9.77	50.0±11.0	32.9±8.80	F(2, 81)=43.5, p<.01	PTSD=PD>HC
BDI	25.61±10.7	13.0±8.32	4.40±4.57	F(2, 81)=51.0, p<.01	PTSD>PD>HC
ASI	30.04±16.1	31.2±12.1	7.26±4.57	F(2, 81)=45.0, p<.01	PTSD=PD>HC
MI	2.20±0.61	2.27±0.81	1.25±0.45	F(2, 76)=24.4, p<.01	PTSD=PD>HC

Note: PDS, Posttraumatic Diagnostic Scale; STAI-State/Trait, Spielberger State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; MI; Mobility Inventory, FDS, Dissociative Experience Scale, ASI, Anxiety Sensitivity Inventory; PTSD, posttraumatic stress disorder; PD, panic disorder; HC, healthy control group.

Table 2. Univariate ANOVAs and post-hoc tests for the study groups on primary and secondary measures

	PTSD	PD	HC	ANOVA		Tukey Post-Hoc
	Mean±SD	Mean±SD	Mean±SD	F	p	
<i>Primary measures (α=.05)</i>						
HP (ms)	762±92.5	823±140	868±125	4.95	.010	PTSD<HC
RSA (ln ms ²)	5.36±0.88	6.13±0.89	6.16±1.17	4.84	.011	PTSD<HC=PD
pCO ₂ (mm Hg)	36.2±2.70	35.1±5.09	38.2±2.73	4.72	.012	PD<HC
CSI (z-scores)	0.14±0.54	0.24±0.57	-0.27±0.71	5.40	.006	PTSD=PD<HC
ESI (z-scores)	0.52±0.70	-0.16±0.78	-0.25±0.49	10.9	.000	PTSD>HC=PD
Sigh rate	0.50±0.51	0.35±0.48	0.21±0.29	6.80 ^a	.033	PTSD>HC ^b
<i>Secondary measures (α=.01)</i>						
lnLF (ms ²)	6.19±0.58	6.48±0.42	6.46±0.59	2.16	.122	
lnVLF (ms ²)	6.13±0.51	6.37±0.37	6.35±0.50	1.88	.160	
Respiratory Rate (c/m)	14.5±3.17	12.4±3.49	12.5±4.07	2.68	.075	
Minute ventilation (L/min)	4.45±1.51	4.19±2.07	3.94±1.54	0.58	.561	
Duty cycle (ratio)	0.48±0.04	0.46±0.04	0.47±0.04	1.41	.249	
Inspiratory flow rate (L/sec)	1.09±0.33	1.08±0.49	0.99±0.34	0.48	.62	
Rib cage contribution (%)	58.9±13.1	63.8±9.21	69.8±12.2	5.81	.005	PTSD<HC
Tidal volume (ml)	340±134	368±191	374±220	0.22	.799	
CD total time	1.37±0.82	1.12±0.60	1.11±0.76	1.00	.374	
CD tidal volume	135±72.1	130±97.7	104±76.1	1.13	.329	

Note. RSA, respiratory sinus arrhythmia; lnLF, natural log of the low frequency; lnVLF, natural log of the very low frequency; pCO₂, end-tidal partial CO₂; HP, heart period; CSI, cardiovascular sympathetic index; ESI, electrodermal sympathetic index; CD, complex demodulation; a=Kruskal-Wallis ANOVA, b=Mann-Whitney-U=206.5, p=.009

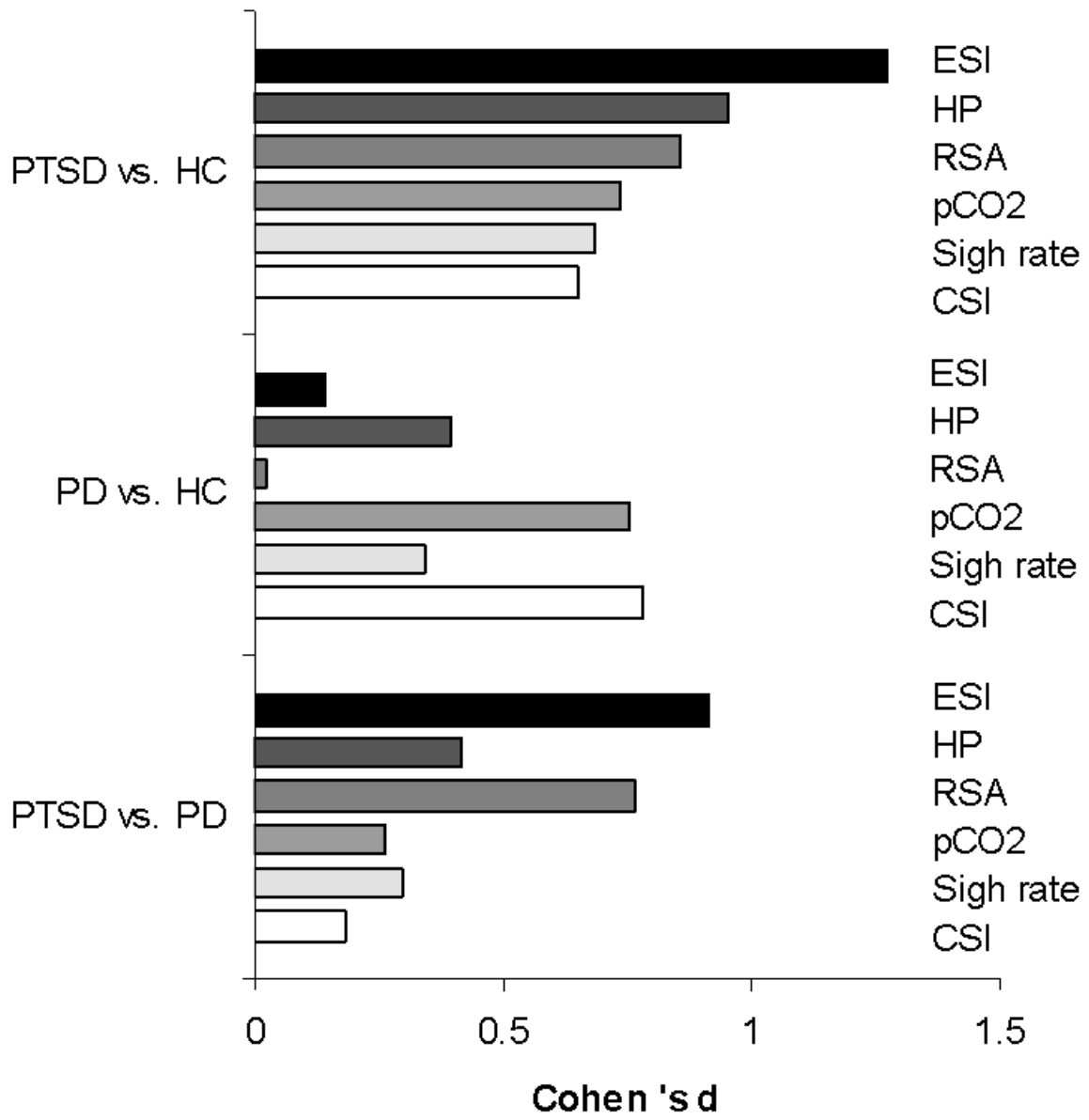
Figure captions

Figure 1. Effect sizes (Cohen's d) for the three group contrasts for all primary measures

Note. ESI, electrodermal sympathetic index (sum of standardized skin conductance level, magnitude and number of non-specific skin conductance fluctuations); HP, heart period; RSA, respiratory sinus arrhythmia; pCO_2 , end-tidal partial CO_2 ; CSI, cardiovascular sympathetic index (sum of standardized T-wave amplitude, pulse wave transit time and pulse wave amplitude); PTSD, posttraumatic stress disorder; PD, panic disorder; HC, healthy control group.

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When Two Paradigms Meet: Does Evaluative Learning Extinguish in Differential Fear Conditioning?

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Abstract

In human classical conditioning, a distinction has been made between signal learning (SL) by which a conditioned stimulus (CS) becomes a predictor for a biologically significant event (unconditioned stimulus, US) and evaluative learning (EL), by which the valence of the US is transferred to the CS. EL, but not SL has been shown to be resistant to extinction. However, this difference has rarely been demonstrated in a single conditioning design. We devised a method of assessing CS valence during a differential aversive conditioning design using coloured pictures as CS and an electric stimulus as US. Half of the participants gave ongoing valence ratings, whereas the other half did not to evaluate effects of these ratings on skin conductance responses (SCRs). Results replicated previous findings of rapid extinction of SCRs. The ongoing valence measurement did not influence SCRs. The findings indicate that EL demonstrated resistance to extinction, although it was not fully preserved.

Introduction

Conditioning accounts of the etiology of anxiety disorders have a long history (Rachman, 1977). While the older, rather simple conditioning models have frequently been criticised, contemporary models can account for most of these criticisms (Davey, 1997). Due to new findings from animal and human studies of Pavlovian conditioning, modern conditioning models provide a rich conceptual framework for the development and maintenance of anxiety disorders (Mineka & Zinbarg, 2006). It has been proposed that *signal learning* (SL, also called expectancy learning) and *evaluative learning* (EL) are two distinct forms of classical conditioning (Baeyens, 1998; Baeyens, Eelen, & Crombez, 1995). This distinction has stimulated research in the emerging field of evaluative conditioning (for an overview see de Houwer, Thomas, & Baeyens, 2001). In a typical evaluative conditioning procedure multiple neutral conditioned stimuli (CS) are paired with clearly positive or negative unconditioned stimuli (US). The magnitude of EL is then measured as the change in valence of the formerly neutral CS in the direction of the US, typically assessed with visual analogue rating scales. The outcome of evaluative conditioning has variably been termed as a preference, attitude or simply “change in liking” which is thought to develop independently of SL (Baeyens, Eelen, Crombez, & Van den Bergh, 1992; but see also Field, 2000).

SL refers to the establishment of a predictive relationship between the CS and the US through repeated contingent pairings of CS and US. SL is typically indexed by psychophysiological measures such as reactions of heart rate and the magnitude of skin conductance responses (SCR). The paradigm, SL is typically studied in, involves two CSs: one CS becomes a signal for the US (the CS+) through contingent pairing. A second CS is presented unpaired (the CS-) and serves as a control stimulus for non-associative processes (Öhman, 1983).

The differentiation of EL and SL is interesting both from a theoretical and a clinical viewpoint. Theoretically, the distinction between the two learning processes rests on their different functional characteristics, including especially their different susceptibility to extinction. EL has been shown to not extinguish as a result of repeated, unpaired presentation of the CS (de Houwer et al., 2001; Diaz, Ruiz, & Baeyens, 2005; Hermans, Crombez, Vansteenwegen, Baeyens, & Eelen, 2002b). This is in sharp contrast to SL which has repeatedly been shown to extinguish rapidly during the extinction training (Hamm, Greenwald, Bradley, & Lang, 1993; Hamm & Vaitl, 1996; Vansteenwegen, Crombez, Baeyens, & Eelen, 1998).

From a more clinical standpoint, the concept of EL and SL as two different processes fits with the clinical observations of persistent negative evaluations even after successful exposure therapy. Imagine, for example, a panic patient with an agoraphobic fear of elevators who not only avoids elevators because he expects to panic inside, but also strongly dislikes elevators. Thus elevators have become signals or predictors of panic (SL) and the patient has additionally developed a strong aversion towards elevators per se (EL). After successful exposure therapy, the signal character of elevators might be extinguished (the patient no longer expects to panic in the elevator), but due to the resistance of EL to extinction the patient's dislike of elevators might persist.

While the distinction between SL and EL as two learning processes within Pavlovian conditioning makes intuitive sense, it is still a matter of debate (De Houwer, Baeyens, & Field, 2005; Diaz, Ruiz, & Baeyens, 2005; Lipp & Purkis, 2005). As indicated above, the experimental paradigms typically used for studying SL and EL differ in a number of respects (e.g., the type and number of CSs and their timing, the nature of the USs, and the dependent variables). These paradigm differences might be a reason why similarities and differences between SL and EL have rarely been studied within one paradigm (Hermans, Vansteenwegen, Crombez, Baeyens, & Eelen, 2002a). A typical EL procedure with multiple CSs and USs does

not permit the measurement of psychophysiological variables. Hence, a test of the similarities and differences between EL and SL requires a differential conditioning design.

This has been done by a number of studies, which used a differential conditioning design, however their focus was on psychophysiological measures. The majority of these studies used as CSs simple stimuli (e.g. geometrical figures, coloured lights) evaluated as neutral prior to conditioning and assessed EL *after* the extinction phase and after electrodermal indicators of SL have extinguished (Hamm, Greenwald, Bradley, & Lang, 1993; Hamm & Vaitl, 1996; Vansteenwegen et al., 1998). The typical finding of more negative ratings for the CS+ after complete extinction of SL was then interpreted as a resistance to extinction of EL in comparison with SL. Similarly, Hermans and colleagues found differential valence ratings both after acquisition *and* after extinction and argued for resistance to extinction of EL (Hermans et al., 2002b). However, because they did not assess psychophysiological measures of SL they cannot compare the extinction rates of EL and SL.

This was pointed out by Lipp and colleagues (Lipp, Oughton, & LeLievre, 2003) who argued that CS valence, like psychophysiological variables, should be measured continuously for each CS presentation if a slower extinction of EL was to be shown. This *online* measurement of valence would provide insight into *the course* of EL and would allow a more precise assessment of its resistance to extinction compared to ratings obtained only before and after the conditioning procedure. Using an electrocutaneous stimulus as US and geometrical shapes as the CSs, they asked participants to operate a dial and pointer device during presentation of each CS to obtain a continuous measure of CS valence. In addition to these *online ratings* they measured valence ratings before and after the procedure, the *pre-/post-ratings*. They found that online ratings of CS valence extinguished at a similar rate as the differential electrodermal responses to the CSs. Interestingly, in the subsequent post-rating phase a difference in the valence of the CS+ and the CS- re-emerged. They explained this reappearance of differential valence ratings as a form of renewal of conditioned responding caused by the context shift from the ongoing conditioning paradigm to the post-rating context (the experimenter entered the room and removed all electrodes

before the post-ratings were completed). Moreover, they concluded that previous findings of resistance to extinction of valence as assessed by pre-post ratings could represent a measurement artefact due to renewal.

However, Lipp et al., (2003) employed very simple CSs as they are typically used in differential conditioning paradigms, such as a circle, a square etc. It was argued that EL effects are most likely obtained with “stimuli that participants feel they can evaluate in an intuitive, spontaneous manner” (De Houwer, Baeyens, & Field, 2005, p. 167). Therefore we decided to take up this question and re-examine the relative rate of extinction of EL and SL. In contrast to Lipp’s design we utilized more complex stimuli as CSs (coloured ink blots) following De Houwer et al., (2005). However, the simultaneous measurement of SL and EL is not easy because skin conductance responses are highly sensitive to novelty, and additional tasks like operating a ratings dial could result in dishabituation (Öhman, 1983). Lipp et al. (2003) used a control group design (in contrast to group “Dial”, the group “No Dial” did not operate the rating dial) to control for the effects of concurrent valence ratings on the post-experimental ratings and SCRs. They found that the rating procedures affected valence, arousal, and electrodermal responding (generally higher second interval responses, and stronger differential responding for first interval responses during extinction). Another possible side effect of concurrent valence ratings could be that they direct participants’ attention to the stimulus contingencies (Baeyens, Eelen, & Van den Bergh, 1990a). Contingency awareness is highly correlated with electrodermal conditioning (Lovibond & Shanks, 2002).

In the light of these findings we designed an online measure of stimulus valence that we expected to exert less influence on electrodermal conditioning and contingency awareness by reducing the frequency of online ratings¹ (only every third CS was followed by a rating procedure as opposed to every CS in Lipp’s study) and gathering the ratings in the time interval between the CS presentations (inter-trial interval, ITI). Following Lipp et al. (2003),

half of our participants were not required to operate the rating dial to test for its effects on differential conditioning of SCR and post-ratings.

Moreover, we re-examined the renewal effect of EL on post-ratings as described by Lipp et al. (2003). If the re-emergence of differential post-ratings was a result of renewal caused by a context shift, a seamless transition from conditioning to post-rating should eliminate this renewal effect. Consequently, we minimized the change of context between the last two measurements (last online rating and post-rating) by having the participants rate all stimuli with the electrodes attached and no intervention of the experimenter.

To summarize, the present study aimed to demonstrate extinction of SL but resistance to extinction of EL (Hypothesis 1). To do so, we devised an unobtrusive online measurement of stimulus valence which allows concurrent assessment of EL and SL. To determine the course of extinction of valence, we employed both within-CS tests (e.g. comparing CS valence during habituation with CS valence during extinction) and between-CS tests (comparing the valence of the CS+ and the CS- at the end of extinction) as typically done in previous studies. Moreover, we expected to eliminate the renewal effect identified by Lipp et al. (2003) by minimizing the context change from the conditioning phase to the post ratings phase (Hypothesis 2). Importantly, as a consequence of our improvements to the method of obtaining valence ratings online during conditioning, we expected the electrodermal conditioning and post-ratings to be unaffected by these measures (Hypothesis 3).

Method

Participants

Thirty-eight female undergraduate Psychology students (mean age = 24.8 old, SD = 6.9) participated for partial fulfilment of course requirements and were randomly assigned to the Dial group (n = 20), whose online valence measurements were obtained during the course of conditioning, or the No Dial group (n = 18), whose valence measurements were obtained during the pre- and post-ratings only. All participants gave informed consent and were instructed that they could decline further participation at any time during the experiment. Participants had no medical history of heart disease, pulmonary disease or any condition that could influence the systems under study.

Materials

Two Rorschach pictures served as CS+ and CS- (counterbalanced across participants). These Rorschach pictures were symmetric, colored inkblots evaluated as equally neutral in preliminary tests. An unpleasant electric stimulus represented the US. A vertical visual analogue scale was used to obtain ratings of stimulus valence (anchors “pleasant” and “unpleasant”) and US expectancy (“Do you believe that this stimulus will be paired with an electric shock?” anchors “No”, “Yes”). Participants operated a rating dial (a linear slider) to respond to these visual analogue scales.

Procedure

The experimenter met each participant individually at the laboratory, which was a temperature-controlled, fully lit, sound-attenuated room that was connected to an adjoining

control room, in which the experimental apparatus was located. The experimenter seated participants in a comfortable armchair 1 m in front of a 19-inch monitor.

Written instructions informed participants that they would be viewing pictures on a computer screen and sometimes feel an electric shock. The experimenter then attached electrodes to the participants as described in the apparatus section below. All electrodes remained attached throughout the whole procedure. In the following, a short film instructed participants about the electrical stimulation. Subsequently, the experimenter individually determined the intensity of the stimulation at a level the participant described as ‘unpleasant and demanding some effort to tolerate’. The experimenter then explained the rating dial the participant would use to rate the CS. The dial consisted of a manual lever that could be moved in a line from the low to the high end to rate the pictures according to scales that would appear on the computer screen.

Pre-rating phase. After the experimenter had left the room the CSs were presented on the screen for 3 s and then immediately followed by the valence scale (half of the participants rated the CS+ first and the other half rated the CS- first). Then, the same procedure was repeated for US expectancy.

Conditioning procedure. The conditioning procedure, which took about 20 minutes, commenced with the following instruction:

“You will now see two pictures on the screen several times. In addition, you will sometimes sense the electrical stimulation you chose before. One of the pictures will sometimes be accompanied by the electrical stimulation. The other picture will never be accompanied by the electrical stimulation”.

The conditioning task consisted of a habituation, an acquisition, and an extinction phase. In each phase, both the CS+ and CS- were presented six times. CS duration was 8 s, and the intertrial interval (ITI) was 18 +/- 2 s (determined at random). During acquisition, each CS+

was immediately followed at stimulus offset by a 500 ms US. Otherwise, all stimuli were presented unpaired.

Online valence ratings. Participants in the Dial group rated stimulus valences in the middle and at the end of each conditioning phase (a total of 12 ratings, 6 for the CS- and 6 for the CS+). Four seconds after CS offset the valence ratings scale appeared on the screen and, after completion of the rating, was followed by the ITI.

Post-rating phase. The post-rating procedure was identical to the pre-rating procedure, except that US expectancy was measured directly after the offsets of the last CS+ and the last CS-. This was done to let participants believe they were still in the extinction phase when they gave US expectancy ratings.

After the post-rating phase contingency awareness was assessed by presenting the CS+ and the CS- along with a control stimulus and asking which of the three ink blots was paired with the US. A recognition measure of contingency awareness was used, as it is considered more sensitive than post-experimental questionnaires that require recall of contingency knowledge (Lovibond & Shanks, 2002). Finally, the experimenter removed all electrodes and orally debriefed the participants.

Apparatus and physiological recordings

An electrical stimulator (constant current unit, Biopac Systems, Inc., Goleta, CA, USA) was used to deliver the US via Ag/AgCl electrodes at the right lower arm. Stimulus delivery and physiological data acquisition were controlled by two personal computers using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and Acqknowledge software (Biopac Systems, Inc., Goleta, CA, USA).

Physiological channels and rating dial information were recorded using the Biopac MP150 system at a rate of 1000 Hz in a continuous mode. Skin conductance was obtained using 11-mm inner diameter Ag/AgCl electrodes filled with isotonic electrode paste (Fowles

et al., 1981). Electrodes were placed on the middle phalanx of the index and the middle finger of the left hand. Two channels were obtained as control measures: body movement was sensed using an accelerometer attached to the left shoulder since it may trigger spurious SCRs and respiration pattern was recorded using one pneumographic bellow at the rib cage to account for spurious SCRs due to deep breaths, coughs, sighs or speech.

Data Reduction and Statistical Analysis

An SCR was calculated by subtracting the average SC level for the 2 s immediately before CS onset from the maximum SC value recorded during the 8 s CS presentation time. An SCR score for the interval containing the UR was computed by subtracting the average skin conductance level within 6 - 8 s following CS onset from the maximum increase in SC level during the 0.5 – 8 s interval following CS offset. SCRs below 0.025 μ S were scored as zero. Artifact correction consisted of visual inspection of respiration and accelerometer channels and exclusion of responses that appeared to be influenced by movement, deep breaths, coughs or sighs. Approximately 2% of responses in each group were excluded. SCR data were normalized using the natural logarithm of 1+SCR. SCR responses to each stimulus type (CS+, CS-) were averaged for three consecutive presentations resulting in 6 blocks for each stimulus type (2 blocks per conditioning phase). Repeated measures ANOVAs were calculated using the SPSS 12 (SPSS Inc., Chicago, IL) General Linear Modeling (GLM) procedure as described in the results section. If the sphericity assumption was not met, a Greenhouse-Geisser correction was computed, with nominal df values being reported. T-tests were used to follow up on significant ANOVA results and effect sizes were reported as Cohens` s d^2 . An alpha level of .05 determined statistical significance.

Results

Resistance to extinction of EL (Hypothesis 1)

Participants' valence ratings of the CS+ and the CS- before (pre-rating), during (online ratings) and after (post-rating) the conditioning procedure are displayed in Figure 1. The first hypothesis (resistance to extinction of EL) involved both between- and within-stimulus tests. Time (time 1, time 2) x CS-type (CS+, CS-) repeated measures ANOVAS were calculated separately for pre/post and online valence measures, and were followed by planned comparisons using t-tests.

Pre/Post valence ratings. Participants gave differential valence ratings on the post-rating but not on the pre-ratings, as indicated by a significant CS-type x Time effect, $F(1, 37) = 11.08$, $MSE = 1164.4$, $p = .002$. Follow-up t-tests indicated that the CS+ was rated more negatively at the post-rating than the CS-, $t(37) = 2.35$, $p = .024$, $d = 0.56$. To determine if the changes within each stimulus were significant, we computed t-tests comparing pre- and post-ratings separately for each CS. Only the CS- changed significantly, decreasing from pre- to post-rating, $t(37) = 2.74$, $p = .009$, $d = 0.47$, hence became more positive. The CS+ did not change significantly in the pre/post ratings, $t(37) = 1.5$, $p = .12$, $d = 0.27$.

Online valence ratings. The 2 (time: late habituation, late extinction) x 2 (CS-type: CS+, CS-) ANOVA revealed a significant CS-type x Time effect, $F(1, 19) = 9.02$, $MSE = 764.9$, $p = .007$ and a significant CS-type effect, $F(1, 19) = 8.86$, $MSE = 1282.9$, $p = .008$. Participants differentially rated the CSs at post-rating only, $t(19) = 3.30$, $p = .004$, $d = 0.84$. In contrast to pre-post ratings, the CS+ increased (became more negative), however at a marginal level of significance, $t(19) = 1.98$, $p = .063$, $d = 0.59$. The CS- did not change significantly, $t(19) = 0.97$, $p = .34$, $d = 0.17$.

One last assessment of extinction of EL tested if the negative valence acquired by the CS+ during acquisition was reduced by the extinction phase. A within stimulus *t*-test for the CS+ compared its valence rating at the end of extinction with its earlier rating at the end of acquisition. The CS+ clearly lost conditioned negative valence, $t(19) = 3.66$, $p = .002$, $d = 0.96$.

Extinction of SL. A *t*-test comparing SCRs to the CS+ and the CS- at the last extinction block was not significant, $t(38)=0.65$, $p = .52$, $d = 0.12$. In contrast to EL, differential electrodermal responses to the CS were lost by the second half of extinction.

-----Insert Figure 1 about here -----

Test of the renewal effect (Hypothesis 2)

A renewal effect would be present if the CS+ and/or the CS- became more negative from the last online valence rating to the subsequent post-rating. Figure 1 indicates that there was hardly any change from online to post-rating. Consistent with hypothesis 2, statistical tests confirmed that neither the CS+ nor the CS- changed from online to post-rating (both $t > .14$), i.e. no renewal occurred.

Influence of online valence ratings on SCR, US expectancy and contingency awareness (Hypothesis 3)

Skin Conductance Responses. As can be seen in Figure 2, SCRs to the CS+ and the CS- in the Dial group and the No Dial group were very similar. This impression was confirmed by statistical analyses. CS-type (CS+, CS-) x Block (first, second) x Group (Dial, No Dial) ANOVAS with repeated measures on CS-type and Block were calculated separately for habituation, acquisition and extinction. During habituation, a significant Block effect indicated the expected habituation of SCRs $F(1, 36) = 22.64$, $MSE = 0.060$, $p < .001$. There

was a weak trend toward higher SCRs to both CSs in the No Dial group, $F(1, 36) = 3.04$, $MSE = 0.014$, $p = .09$. Regarding acquisition, a significant CS-type factor indicated robust differential conditioning (higher responses to the CS+ than to the CS-), $F(1, 36) = 23.50$, $MSE = 0.005$, $p < .001$. During extinction, a CS-type main effect was modulated by a CS-type x Block interaction, $F(1, 36) = 4.69$, $MSE = 0.004$ $p < .037$ and $F(1, 36) = 4.432$, $MSE = 0.002$, $p = .04$, respectively. The CS+ elicited stronger responses than the CS- during early but not during late extinction. The factor Group was not significant during acquisition or extinction, both $F < 0.24$ ³. A 6 (Time) x 2 (Group) ANOVA with repeated measures on the Time factor analysed unconditioned responses to the US during acquisition. Only the Time effect reached significance, $F(5, 180) = 12.55$, $MSE = 0.011$, $p < .001$.

Post-ratings of US expectancy and CS valence. US expectancy rated immediately after the last CS+ and the last CS- were analysed using a 2 (group: Dial, no Dial) x 2 (CS-type: CS+, CS-) ANOVA. The CS-type factor approached significance, $F(1, 36) = 3.01$, $MSE = 3473.7$, $p = .09$ and no significant effects were obtained for the group factor, $F(1,36) = 1.22$. Differential US expectancies had largely extinguished in both groups. The post-ratings of CS valence revealed a significant CS-type effect, $F(1, 36) = 5.26$, $MSE = 2830.6$, $p = .03$ and no group effect, $F(1,36) = 0.64$.

Contingency awareness. Two participants (5.3%) in the Dial group and no participants in the No Dial group failed to identify the CS+ at the recognition test following extinction, $\chi^2(1) = 1.9$, $p = .17$.

-----Insert Figure 2 about here -----

Discussion

Until recently, SL and EL have been studied in separate research designs. Investigation of both types of learning in a single paradigm is desirable both for the progression of learning theories and for the extension of models of anxiety disorders. We developed a measure of EL that leaves the SL-process unaffected but provides a detailed insight into the evaluative-affective learning curve. We were also able to demonstrate how the previously observed renewal effect for post-ratings (Lipp et al. 2003) could be circumvented.

The distinction between EL and SL is based partially on the relative resistance to extinction of EL compared to SL (de Houwer et al., 2001; Diaz et al., 2005; Hermans et al., 2002b). In line with our expectations, participants continued to evaluate the CS+ more negatively than the CS- after extinction. However, it was not quite clear which CS “did the work”, i.e. which CS changed significantly over the course of the conditioning procedure. While online ratings of valence showed changes mainly for the CS+, post-ratings of valence identified significant changes primarily for the CS-. Drawing on conceptualisations of differential aversive conditioning, changes would be expected primarily for the CS+. Hermans and colleagues have repeatedly found effects of conditioning on the valence of both CSs after acquisition: while the CS+ became negative the CS- became positive, together constituting robust differential conditioning (Hermans et al., 2002b; Hermans et al., 2002a). One of these studies (Hermans et al., 2002b) also assessed extinction. Their differential valence effect measured after acquisition remained relatively stable across the extinction phase, which is in contrast to our result of marked reduction of negative valence of the CS+ during extinction. Procedural differences may account for this discrepancy. Besides shorter ITIs and a higher number of CS presentations, Hermans et al. (2002a, b) used individually selected, neutral pictures of human faces as CSs. One may speculate that evaluations of

human faces may involve additional processes, like for example the need for consistency (Davey, 1994) which does not apply to ratings of Rorschach pictures.

On a procedural level, in contrast to Hermanns' studies our paradigm was more similar to Lipp's design (Lipp et al. 2003). Similar to our results, they found extinction of the negative valence of the CS+, and neutral ratings for the CS+ by the end of the extinction phase. Also consistent with our results is the small albeit significant difference between the CS+ and the CS- at the end of extinction in their Experiment 1.

The ambiguous findings regarding the course of EL highlights the lack of a clear definition of how to test for resistance to extinction. Should only the changes within a CS be considered (e.g. change within the CS+ from habituation to extinction), or should the difference between CS+ and CS- after extinction be considered? This latter test appears inappropriate if the extinction rate of EL is to be directly compared to electrodermal indicators of SL. EL effects in the positive direction (in case of the CS-) and in the negative direction (in case of the CS+) can be treated additively. In contrast, SCRs are unidirectional in that skin conductance only deflects in the upward direction which is then interpreted as anxious arousal. Thus responses to the CS- can only reduce the difference between the CSs but not increase it as in EL.

Alternative indicators of EL from the autonomic response domain are the electromyographic responses from the eye-blink startle reflex or the musculus corrugator, which both have been shown to be sensitive to positive and negative valence (Lang, Greenwald, Bradley, & Hamm, 1993; Larsen, Norris, & Cacioppo, 2003; Vansteenwegen et al., 1998). Alternatively, Hermanns and colleagues have proposed to use US expectancy ratings as an indicator for SL (Hermanns et al., 2002b). This approach appears highly plausible as EL and SL would both be measured within the verbal-cognitive response domain. Still,

genuine preparatory psychophysiological responses would only be partially captured by this approach⁴.

Regarding our second hypothesis, we found that the renewal effect identified by Lipp can be circumvented if post-ratings of valence are conducted in the same context as the online valence ratings (without removing electrodes or giving instructions in between). However this cannot preclude that renewal played a role in studies examining EL with post-conditioning paper-pencil tests as argued by Lipp et al. (2003). It has been shown repeatedly that extinction of autonomic measures is highly sensitive to changes in context (Bouton, 1994; Milad, Orr, Pitman, & Rauch, 2005; Neumann, Lipp, & Cory, 2006; Vansteenwegen et al., 2005). Because we have not directly manipulated context change in our design, we can not determine the specific conditions of this renewal effect.

We demonstrated that a concurrent measurement of stimulus valence provides useful insights into the course of EL in a differential conditioning design. At the same time the specific pattern observed for online valence ratings suggests that several processes influence these evaluations, only one of them being intrinsic valence changes. For example, the obvious reduction of negative valence during the habituation phase for both CSs suggests that arousal is one such factor. As repeated unpaired CS presentations reduce this arousal (as indicated by SCRs), participants evaluated the CSs more positively. Alternatively this change could be due to the mere exposure effect, i.e. the gradual increase in liking of a stimulus due to familiarisation. The mere exposure effect is strongest over the first few presentations and levels off thereafter (Bornstein, 1989). Yet another possibility is that participants need for consistency (Davey, 1994) exerts influence on the changes of their valence ratings.

As expected, almost all of our participants correctly verbalized the CS-US contingency. They also assigned somewhat higher expectancies of shock to the CS+ after the extinction procedure. In contrast to traditional EL-paradigms with multiple stimuli, EL in a

differential conditioning design necessarily takes place in full awareness of the contingencies. This increases the likelihood of demand awareness, i.e. that participants become aware of the study aim. While EL has been found repeatedly to be independent of contingency awareness (Field, 2000; but see also Purkis & Lipp, 2001), less is known about the robustness of the EC effect when contingency awareness is fully present as in Pavlovian conditioning designs. Recent evidence from the evaluative conditioning paradigm indicates that the presence of contingency awareness could even cause a reactance effect (i.e., changes in the opposite direction of the valence of the CS) and that this reactance effect is sometimes outside of conscious control (Hammerl & Fulcher, 2005). While the use of an affective priming procedure sometimes serves as a remedy here (Hermans et al., 2002b; Hermans et al., 2002a; Vansteenwegen, Francken, Vervliet, De Clercq, & Eelen, 2006), it interrupts the conditioning procedure and is not suitable as a continuous measure of stimulus valence. De Houwer Baeyens and Field (2005) suggest that different processes underlie EL effects obtained in EL paradigms (characterized by low contingency awareness) and differential conditioning paradigms (characterized by high contingency awareness). Therefore they might be governed by different principles during extinction: in differential paradigms reduction of negative valence as a result of decrementing US expectancy, in evaluative conditioning paradigms resistance to extinction due to intrinsic changes of valence.

New conditioning designs are needed if EL and SL were to be characterized and compared. In addition, future research should address the potential confounding factors influencing the repeated assessment of stimulus valence. We have discussed the mere exposure effect (Bornstein, 1989), the need for consistency (Davey, 1994), demand awareness/reactance (Field, 2000; Hammerl & Fulcher, 2005), and the frequency of judgements (Catena et al, 1998).

Some limitations to the present findings have to be considered. We did not include an affective priming procedure after conditioning to ensure that evaluative ratings were not

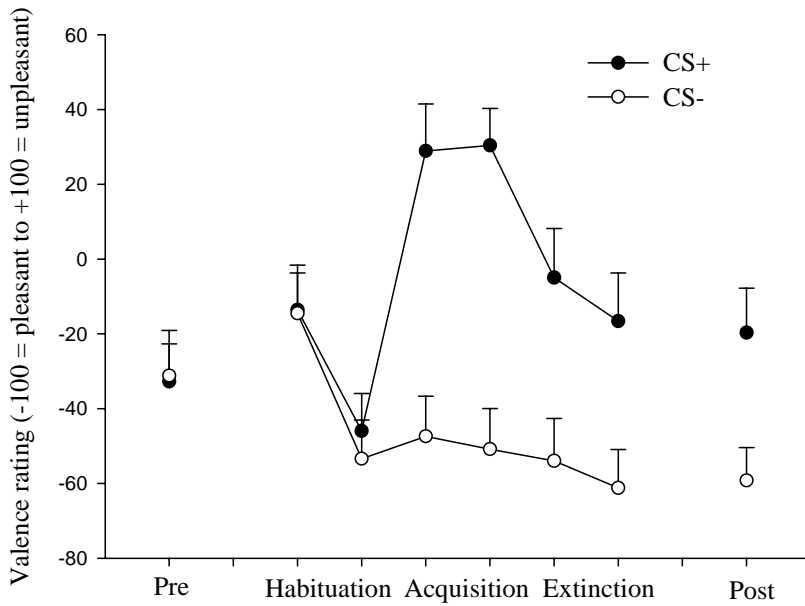
influenced by demand characteristics. In contrast to the studies that found good correspondence between affective priming and evaluative ratings, the higher frequency of valence ratings in our design could have increased demand awareness. Also, our extinction procedure was relatively short in comparison to other study designs. The possibility exists that EL would extinguish completely with a longer extinction phase (see Lipp et al., 2000, Experiment 2). Finally, we used only female participants. However, to our knowledge, previous studies have not reported significant gender effects with respect to EL, so one might expect that our results would hold for both genders.

Despite these limitations, we argue strongly for including concurrent measures of EL in studies of differential conditioning. Evidence from recent fear conditioning studies indicate that EL is relevant to affective learning in panic disorder and posttraumatic stress disorder (Blechert, Michael, & Wilhelm, in preparation; Michael, Blechert, Vriends, Margraf, & Wilhelm, submitted). Moreover, conditioning models of anxiety disorders encompassing affective-evaluative learning processes could also inspire progress in exposure therapy for these disorders. Imagine the panic patient introduced above saying: “since my therapy I use the elevator whenever I can. It gives me some time of my own to breathe and relax....”.

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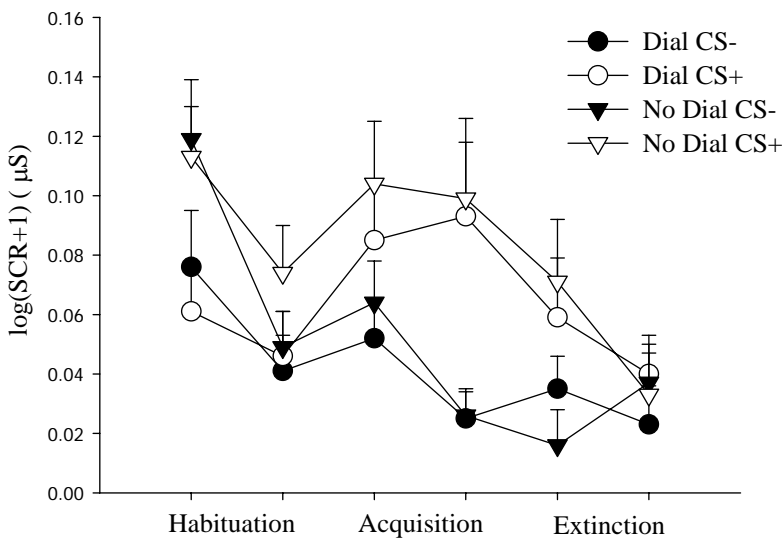
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Figure 1. Means and standard errors of valence ratings for the CS+ and the CS- at pre-/post-rating and online ratings during the conditioning procedure



Note: Pre = Pre-rating, Post = Post-rating

Figure 2. SCRs (means and standard errors) to the CS+ and the CS- in the Dial group and the No Dial group during the conditioning procedure



Footnotes

¹ In the field of causal judgement, studies have identified a “frequency of judgement effect” (Catena, Maldonado, & Candido, 1998; Collins & Shanks, 2002). This effect refers to the observation that judgements of contingency between a possible cause and an effect (e.g. a fictitious symptom and a disease) become more inaccurate as the frequency of contingency ratings increase, possibly because participants base their rating more on the last covariation information they received. Assuming that a similar effect applies to online valence ratings, this was an additional reason to reduce the frequency of online valence ratings in the present study.

² We used the formula Cohen's $d = (M_1 - M_2) / \sigma_{\text{pooled}}$ where $\sigma_{\text{pooled}} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$ for both between and within-subject t-tests as recommended by Dunlop, Cortina, Vaslow, & Burke, 1996

³ We conducted separate analyses for first and second interval responses (time windows 0-4 s and 4-8 s respectively) and found very similar results with respect to the group effect. Results are available from the authors on request.

⁴ Although SCRs and online US expectancy ratings are highly correlated, they are not in perfect agreement (e.g. Lovibond, 2004). We found a trend of differential US expectancy ratings at the end of extinction, while SCRs had completely extinguished by this time.

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**FEAR CONDITIONING IN POSTTRAUMATIC STRESS DISORDER: EVIDENCE
FOR DELAYED EXTINCTION OF AUTONOMIC, EXPERIENTIAL, AND
BEHAVIOURAL MEASURES**

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Abstract

Aversive conditioning has been proposed as an important factor involved in the aetiology of posttraumatic stress disorder (PTSD). However, is not yet fully understood exactly which learning mechanisms are characteristic for PTSD.

PTSD patients (n=36), and healthy individuals with and without trauma exposure (TE group, n=24; nTE group, n=34), underwent a differential fear conditioning experiment consisting of a habituation, acquisition, and an extinction phase. An electrical stimulus served as the unconditioned stimulus (US), and two neutral pictures as conditioned stimuli (CS+, paired; CS-, unpaired). Conditioned responses were quantified by skin conductance responses (SCRs) and, in addition to previous studies, by subjective ratings of CS-valence and US-expectancy, and a behavioural test.

In contrast to the nTE group, PTSD patients showed delayed extinction of SCRs to the CS+. Ratings of valence and US-expectancy as well as the behavioural test confirmed this pattern. These findings point to a deficit in extinction learning in PTSD. In addition, more PTSD patients than control participants failed to report the CS-US contingency, thereby providing preliminary evidence of reduced discrimination learning in PTSD.

Reduced extinction learning, and possibly also deficient discrimination learning appear to be important learning mechanisms in PTSD.

1 Introduction

Posttraumatic stress disorder (PTSD) is a pervasive psychiatric condition characterized, *inter alia*, by symptoms of persistent re-experiencing of the traumatic event (DSM-IV, American Psychiatric Association, 1994). Contemporary theories of PTSD concur in assuming that memory and learning processes like perceptual priming and fear conditioning underlie these re-experiencing symptoms (Michael et al., 2005, Kolb, 1984; Pitman 1988, 1989; Rothbaum & Davis, 2003). According to the fear conditioning approach, the traumatic event (unconditioned stimulus, US) triggers an unconditioned response (UR) which is characterized by strong arousal and intense fear. This UR becomes associated with cues, such as smells, voices, or sights (conditioned stimuli, CSs) which were present during the traumatic event. As a result of this pairing, these cues can trigger similar responses (conditioned responses, CRs) even in the absence of the original US. Thus, re-experiencing symptoms can be understood as CRs, which remain persistent, even in the absence of the US.

However, the major question remains: why do these symptoms disappear in the aftermath of a traumatic event in most individuals, but persist in those who develop PTSD? Within the conditioning framework, three accounts have been put forward to answer this question: enhanced conditionability, reduced conditioned inhibition, and reduced discrimination learning.

The concept of *enhanced conditionability* refers to a hypothetical trait predisposing to the development of stronger CRs to a traumatic event, and/or to a reduced ability to extinguish these CRs (Orr et al., 2000). Experimentally, conditionability is typically assessed in a differential fear conditioning paradigm in which one CS is paired with the US during the acquisition phase (the CS+) and another CS is not (the CS-). During a subsequent extinction phase, both CSs are presented without the US. The difference between reactions to the CS+ and the CS- is taken as a measure of conditionability and is referred to as differential or

discriminative learning. If this differential responding is enhanced during acquisition, or does not extinguish during extinction, it is thought to predispose an individual to the development of PTSD subsequent to trauma exposure.

However, conditionability, as assessed by differential fear conditioning, actually confounds two processes: excitatory conditioning and inhibitory conditioning (assessed by responses to the CS+ and the CS-, respectively) which each may be informative in its own right (Lissek et al., 2005). In fact, it has been suggested that the inability to inhibit fear in the presence of safety cues (i.e. the CS-) causes excessive fear responses in PTSD patients (Davis, Falls, & Gewirtz, 2000; Grillon & Morgan, 1999; Rothbaum & Davis, 2003). Thus, it is proposed that PTSD patients should differ from controls mainly because of poor inhibitory processes, i.e. they should show heightened responding to the CS-. In the following we will refer to this account as *conditioned inhibition account* (footnote 1).

In support of the enhanced conditionability account, Orr and coworkers demonstrated enhanced conditionability in PTSD as represented by stronger differential responding during acquisition and extinction (Orr et al., 2000). Similarly, Peri and colleagues found enhanced differential effects during extinction in PTSD patients (Peri, Ben-Shakhar, Orr, & Shalev, 2000). However, the same two studies also found heightened reactions in PTSD with respect to the CS- during acquisition, and in the study by Peri and colleagues, this heightened responding to the CS- was still present during extinction. Although these two studies interpreted their findings to support enhanced conditionability in PTSD, they are also partially consistent with the conditioned inhibition account.

In addition to these two accounts, a third conceptualisation of *reduced discrimination learning* has received support in the clinical conditioning literature. Investigating eye blink conditioning (footnote 2) in combat veterans with and without PTSD and control participants, Ayers, White and Powel (2003) found differential responding to the CSs only in control participants. They attributed this to impaired discriminative learning in combat veterans,

possibly due to general memory deficits. However, in a study of the effect of hydrocortisone in eye blink conditioning, Vythilingam et al. (2006) found equal discriminative learning in PTSD and control participants in their placebo condition. Grillon and Morgan (1999) measured the fear potentiated startle reactions in a differential fear conditioning paradigm in two separate sessions. In contrast to controls, PTSD patients failed to acquire differential conditioning during the first session. During the second conditioning session one week later, both groups showed differential responding, and the PTSD group demonstrated higher startle reactions during baseline before conditioning. The authors suggest that this slowed discriminative learning in PTSD led to enhanced context conditioning. In contrast to the enhanced conditionability account, the discriminative learning account highlights that this type of learning can be seen as a highly functional process by which participants learn to identify reliable threat signals for the US (Grillon, 2002a) and distinguish between safe and unsafe conditions.

At this stage, research has yielded partial support for the enhanced conditionability account of PTSD. While some studies were supportive of this view (Orr et al., 2000; Peri et al., 2000) others found equal (Vythilingam et al., 2006) or impaired discrimination learning (Grillon & Morgan, 1999, Ayers et al., 2003). In addition, the conditioned inhibition account, predicting enhanced responding in PTSD patients to the CS-, has not been explicitly addressed in previous fear conditioning studies of PTSD.

To date, conditioning studies in PTSD have focused primarily on implicit indicators of conditioning, such as SCRs or the fear potentiated startle. However, this focus on implicit measurements unnecessarily confines the window of scientific inquiry and disregards the domains of verbal-cognitive and behavioral responses. Contemporary conditioning models highlight the role of cognitive processes (Chan & Lovibond, 1996; Davey, 1997; Reiss, 1991) and affective valence appraisals (Hermans, Vansteenwegen, Crombez, Baeyens, & Eelen, 2002). According to the expectancy model of fear conditioning (Reiss, 1991) individuals

continuously and explicitly adjust their expectancies regarding the likelihood of the US when the CS+ and the CS- are repeatedly presented. A growing number of studies have successfully included continuous 'online' measures of US-expectancy (e.g. Lovibond, Davis, & O'Flaherty, 2000; Neumann, Lipp & Cory, 2006; Vansteenwegen et al., 2006). Another important process involved in human conditioning relates to conditioned changes in affective valence appraisals of the CSs, a process called evaluative conditioning (de Houwer, Thomas, & Baeyens, 2001). According to this theory, affective valence is transferred from the US to the CS as a result of paired presentations during conditioning.

In this study we examined differential fear conditioning in PTSD patients using a more comprehensive set of dependent measure which assessed autonomic (SCRs), affective (valence ratings), and cognitive (US-expectancy ratings) responses. As a subsidiary aim we explored if conditioned responding also generalizes to the behavioural domain using a behavioural forced choice test (Michael, Blechert, & Vriends, unpublished data). In order to maximise the conclusiveness of between-group comparisons, we included two healthy control groups, with or without trauma exposure (TE group, nTE group, see also Peri et al., 2000). The accounts of heightened conditionability, conditioned inhibition, and reduced discrimination learning were evaluated. To do so, statistical analyses assessed differential conditioning but also included single-CS analyses. The enhanced conditionability account would predict larger differential reactions (i.e. stronger SCRs to the CS+ but not to the CS-) in the PTSD group compared to the other two groups while the account of reduced discrimination learning would predict the opposite (a smaller difference between SCRs to the CS+ and the CS-). The conditioned inhibition account would predict enhanced responding to the CS-.

2 Method

2.1 Participants

We recruited three study groups: the PTSD group consisted of 36 adults qualifying for a primary diagnosis of current chronic PTSD according to the DSM-IV (American Psychiatric Association 1994), the TE group consisted of individuals who had been exposed to a traumatic event without developing PTSD (n=24), and the nTE group consisted of healthy individuals, who had never been exposed a traumatic event (n=34). Participants were included into the TE group if they fulfilled the A-criterion of the DSM-IV diagnosis of PTSD but reported no current mental disorder. However, past disorders other than an anxiety disorders were accepted. Three participants in the TE group fulfilled sub-clinical PTSD (one of the B-F criteria unfulfilled). Healthy participants did not report any current or past mental disorder. Further exclusion criteria for all participants were: lifetime history of psychosis, bipolar disorder, mental disability, drug abuse or dependence, a medical history of conditions that might affect the physiological systems under examination (e.g., angina, myocardial infarction), use of medication with strong autonomic effects, age of less than 18 or more than 65 years. Trauma types in the PTSD and the TE group were accidents (traffic and work-related; n=11 in the PTSD group, n=8 in the TE group), physical or sexual violence (11, 6), natural disasters (2, 2), war-related traumata (e.g. imprisonment, torture; 3, 1), life threatening illness (2, 1) and other traumata (7, 6). Trauma type were equally distributed across both groups, $\chi^2(5)=1.62$, $p>.05$.

The diagnosis was assessed using the F-DIPS ('Diagnostic Interview for Mental Disorders – Research Revision'; Margraf, Schneider, Soeder, Neumer, & Becker, 1996), a well-validated structured interview for diagnosing DSM-IV disorders. The F-DIPS is a modified German version of the Anxiety Disorder Interview Schedule for DSM-IV – Lifetime version (ADIS-IV-L; DiNardo, Brown, & Barlow, 1994), which is widely used for the

assessment of anxiety disorders and shows excellent psychometric properties (Brown, DiNardo, & Lehman, 2001). The F-DIPS further contains diagnostic modules for mood and substance-related disorders, as well as a screening for schizophrenia and other psychotic disorders.

Participants were either referred to us by collaborating mental health institutions or responded to advertisements in the local press. If patients were taking psychoactive drugs, inclusion required that they had been on a constant regimen for at least two weeks before testing, in order to avoid possible side effects or withdrawal symptoms due to dose alternations. Six patients reported occasional use and two patients regular use of benzodiazepines. Patients who used benzodiazepines occasionally were asked not to do so on study days. Nine patients took selective serotonin or noradrenaline reuptake inhibitors and two patients took tricyclic antidepressants. Participants were told to abstain from alcohol for 24 hours before testing. The following secondary disorders were diagnosed in the PTSD group: major depression (n=11), panic disorder with or without agoraphobia (n=9), social phobia (n=4), pain disorder (n=4), generalized anxiety disorder (n=3), and dysthymic disorder (n=2).

Anxiety and depressive symptoms were assessed with the German versions of the State-Trait Anxiety Inventory (STAI, Laux et al 1981) and the Beck Depression Inventory (BDI, Hautzinger et al 1994). In the PTSD and the TE group, PTSD symptoms and dissociative symptoms were assessed with the Posttraumatic Diagnostic Scale (PDS, Stieglitz, Nyberg, Albert, Frommberger, & Berger, 2002) and the Dissociative Experiences Scale (DES, Freyberger et al., 1998).

The study was approved by the local ethics committee and participants gave written consent before participating. Each participant received a payment of 90 CHF (approximately 70 USD).

2.2 Procedure

Following the diagnostic assessment, eligible participants participated in an implicit evaluative conditioning task, the results of which will be presented elsewhere (Michael, Vriends, Blechert, & Margraf, in preparation). One week thereafter, the current experiment was conducted. On arrival, electrodes were attached and participants watched a short film instructing them about the stepwise adjustment of the electrical stimulation. The film depicted a participant and the experimenter adjusting the level of electric current. Together with the experimenter, participants then adjusted the intensity of the stimulation to a level which they described as being ‘unpleasant and demanding some effort to tolerate’. For 5 minutes thereafter, participants sat quietly and given time to adapt to the laboratory environment and the electrodes. Then the usage of the rating dial was explained and participants gave a retrospective rating of the US aversiveness (anchor labels as indicated on the computer screen: “-100=very slightly unpleasant” to “+100=extremely unpleasant/painful”). The conditioning task commenced with the instruction that two pictures would be shown on the screen in random order and that only one of the pictures would occasionally be accompanied by the electrical stimulation. Two pictures of coloured symmetrical pictures (Rorschach inkblots) served as CS+ and CS- (counterbalanced across participants). The conditioning task consisted of a habituation, acquisition, and an extinction phase. In each phase, the CS+ and CS- were each presented six times. CS duration was 8 s and the intertrial interval was 18 +/- 2 s (determined at random). During acquisition, each CS+ was immediately followed at stimulus offset by a 500 ms US.

During the conditioning procedure, ratings of US-expectancy and stimulus valence were repeatedly obtained. After CS offset, participants were asked to rate whether they expected this particular CS to be followed by the US, by means of a visual analogue scale (“Do you believe that this stimulus will be paired with an electric stimulation?” anchors “No”, -100; “Yes”, 100). Three ratings for each CS were obtained at the end of the habituation,

acquisition, and extinction phase. These US-expectancy ratings were followed by valence ratings of the corresponding CS (“pleasant”, -100; to “unpleasant”, 100). Additional valence ratings were obtained in the middle of each conditioning phase, resulting in six valence ratings for each CS. A previous study established that these ratings do not influence the psychophysiological outcome variables in a differential aversive conditioning paradigm (Blechert, Michael, Williams, & Wilhelm, submitted; see also Lipp, Oughton, & LeLievre, 2003). Following extinction, contingency awareness was assessed by a screen presenting the CS+, the CS-, and a control stimulus. The participants were prompted to select the ink blot which was previously paired with the US. The experimenter then entered the room with a bowl containing 20 chocolate bars (50% depicting the CS-picture and 50% depicting the CS+ picture) and asked them to pick one chocolate bar „as a small token for your participation”. Selection of the chocolate bar depicting CS- was interpreted as avoidance of the CS+. Finally, all electrodes were removed, participants were orally debriefed and patients were given information regarding treatment opportunities in the surrounding area.

2.3 Apparatus and Physiological Recordings

The experiment took place in a temperature-controlled, fully lit, and sound-attenuated room, which was connected electronically to an adjacent control room, in which the experimental apparatus was located. Participants were seated in a comfortable armchair placed 1 m in front of a 19-inch monitor with a refresh rate of 100 Hz. An electrical stimulator (constant current unit, Biopac Systems, Inc., Goleta, CA, USA) was used to deliver the US via Ag/AgCl electrodes on the right lower arm. Stimulus delivery and physiological data acquisition were controlled by two PCs running E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and Acqknowledge software (Biopac Systems, Inc., Goleta, CA, USA). Physiological channels and rating dial information were recorded at a rate of 1000 Hz in continuous mode using the Biopac MP150 system. Skin conductance was obtained using 11-mm inner diameter

Ag/AgCl electrodes filled with isotonic electrode paste (Fowles et al., 1981). Electrodes were placed on the middle phalanx of the index and middle finger of the left hand. Subjective ratings of the stimuli were measured with a rating dial on which a vertical visual analogue scale was affixed with the lower label -100 and the upper label +100. The scale corresponded to the ones being displayed on the computer screen, indicating the verbal anchors of the scale to be rated. Two channels were obtained as control measures: body movement was assessed using an accelerometer attached to the left shoulder, since movement may trigger spurious SCRs; respiration pattern was recorded using two pneumographic bellows, one at the rib cage and one at the abdomen, to account for spurious SCRs due to deep breaths, coughs, sighs or speech.

2.4 Data reduction and statistical analysis

An SCR was calculated by subtracting the average skin conductance level (SCL) for the 2 s immediately before CS onset (baseline) from the maximum SCL recorded during the first 4 s (first interval response, FIR [footnote 3]) of the 8 s CS presentation time. The UR to the electric stimulation was computed by subtracting the average SCL during the last 2 s of the CS presentation from the maximum SCL recorded during the 8 s following the US. SCRs below 0.025 μ S were scored as zero and square root transformation was applied to normalise the distribution of SCRs. Artefact correction for the SCRs consisted of a careful visual inspection of respiration and accelerometer channels and the manual exclusion of SCRs which appeared to be influenced by movement, deep breaths, coughs or sighs. SCR responses to each stimulus type (CS+, CS-) on three consecutive presentations were averaged, resulting in two blocks per conditioning phase (e.g. first and second half of habituation) for each stimulus type. Two indices of electrodermal responding during habituation were computed to be used as covariates in the subsequent analyses: mean SCL during habituation (SCL_{hab}) was estimated by averaging the 2-s baselines preceding the twelve habituation CS presentations.

Likewise, SCRs to both CSs were averaged across all habituation CS presentations as an index of orienting responses (SCR_{hab}).

Statistical Analyses. Separate analyses were conducted for each outcome measure and each conditioning phase. Repeated measures ANOVAS were calculated for the between subjects factor Group (three levels for the omnibus test and two levels for the group contrasts) and the within subject factors CS-type (CS+, CS-) and Time (first vs. second half of phases) using the SPSS 12 (SPSS Inc., Chicago, IL) General Linear Modeling procedure. Analyses of US-expectancy ratings did not involve the Time factor because only one measurement was taken per conditioning phase. To specifically assess the differences between the three groups, significant between group effects in the omnibus analyses were followed by three planned comparisons (PTSD vs. nTE group, PTSD vs. TE group, and TE group vs. nTE group) using Time X CS-type X Group ANOVAS. The accounts of enhanced and reduced discriminative learning would predict interaction effects of the factors Group with CS-type and/or Time in these comparisons. When the Group effect reached significance these pairwise ANOVAS were broken down per stimulus to evaluate the conditioned inhibition account which would predict heightened responding of the PTSD group to the CS- in comparison with the control groups. This was done by calculating Group X Time ANOVAS separately for the CS+ and the CS-. If the sphericity assumption was not met, a Greenhouse-Geisser correction was computed, with nominal df values being reported. An alpha level of 0.05 determined statistical significance.

3 Results

3.1 Demographics, psychometrics and control variables

There were equal percentages of female participants in the PTSD, the TE group and the nTE group (72.2%, 54.2%, 73.5%, respectively, $\chi^2(2, 94)=2.88, p=.24$). Table 1 shows demographic, psychometric, and control measures for the three groups. Groups did not differ in age and years of education. In accordance with the diagnostic categorisation, the PTSD group scored higher than the control groups on the PDS, FDS, STAI, and the BDI. PTSD patients selected a lower US level than both control groups, but subjective ratings of US intensity did not differ between groups. PTSD patients also showed generally higher SCRs during habituation and a trend to higher URs compared to the nTE group.

Contingency awareness. The results of the recognition test of contingency awareness indicated that 19 out of the 94 participants were unable to correctly identify the CS+ after extinction (i.e. were unaware of stimulus contingencies). This classification was verified by analysing the US-expectancy ratings at the end of acquisition in aware and unaware participants: an Awareness (aware, unaware) X CS-type (CS+, CS-) ANOVA yielded a significant Awareness X CS-type interaction, $F(1, 92)=11.92, p=.001$, which indicated higher differential US-expectancy ratings (higher ratings for the CS+ than for the CS-) in aware participants, but not in unaware participants. There were more unaware participants in the PTSD group than in the trauma or the nTE group ($n=12/2/5$ respectively, $\chi^2(2)=6.58, p=.037$). Exploratory analyses compared aware and unaware PTSD patients on the psychometric measures. Unaware PTSD patients had slightly increased BDI scores, $M_{\text{unaware}}=23.9 (7.73)$, $M_{\text{aware}}=30.9 (10.1)$, $t(25)=2.00, p=.056$. Awareness of contingencies is considered a critical prerequisite for successful electrodermal conditioning (Lovibond & Shanks, 2002; Purkis & Lipp, 2001), but is thought to be less relevant for evaluative conditioning (Baeyens, Eelen, Crombez, & Van den Bergh, 1992; Baeyens, Eelen, & Van den Bergh, 1990). Therefore we

excluded unaware participants from the analyses of SCRs. Moreover, research has repeatedly demonstrated that a significant proportion of participants do not respond electrodermally to conditioning, (non-responders, see also LaBar & Phelps, 2005; Milad, Orr, Pitman, & Rauch, 2005; Olsson & Phelps, 2004; Schell, Dawson, & Marinkovic, 1991). Accordingly, we excluded participants who did not show measurable SCRs at all and participants who did not respond to the CSs during any acquisition or extinction trial. Non-responders were equally distributed across groups, $n=6/5/3$ for PTSD, TE, and nTE group, respectively, $\chi^2(2)=1.75$, $p=0.48$.

-----Insert table 1 about here-----

3.2 Conditioning Procedure

3.2.1 Omnibus analyses (PTSD vs. TE group vs. nTE group)

Figure 1 displays means for all three study groups for the CS+ and the CS- during early and late phases of habituation, acquisition, and extinction. Omnibus ANOVAS *across all three groups* yielded significant between group effects for SCRs during acquisition, $F(2,62)=4.12$, $p=.021$, and extinction, $F(2,62)=4.19$, $p=.020$. Likewise, Group effects were significant for valence ratings during habituation, $F(2, 91)=3.49$, $p=.035$, acquisition, $F(2, 91)=3.19$, $p=.046$, and extinction, $F(2, 91)=5.82$, $p=.004$, as well as for US-expectancy during extinction, $F(2, 91)=4.52$, $p=.013$. Thus, follow-up analyses involving pairwise group comparisons (i.e. PTSD vs. TC, PTSD vs. nTC, and TC vs. nTC) were computed for all measures.

Table 2 lists the results of the ANOVAS of the three pairwise comparisons of the three groups. The columns of Table 2 display the effects of the factors Group (between group effects, $df=1$), CS-type (CS-type effects indicate differential conditioning, i.e. higher responses to the CS+ than to the CS-), and Group X CS-type interactions. Significant effects

of the factor Group were followed by separate ANOVAS for the CS+ and the CS-, (column 'Post-hoc' in Table 2). For the sake of brevity, significant effects of the factor Time are reported in the text only when it interacted with the group variable.

As can be seen from column 'CS-type' of Table 2, differential conditioning effects were present in all groups and for all measures during the acquisition and the extinction phase. This indicated successful discrimination learning in all three study groups.

-----Insert figure1 about here-----

-----Insert table2 about here-----

3.2.2 Comparison of the PTSD group and the nTE group

SCR. No significant effects involving the factor Group were found during habituation. During acquisition, significant Group and CS-type effects emerged which were modulated by a Group X CS-type X Time interaction $F(1, 46)=4.57, p=.038$ (not shown in Table 2). This interaction pointed to stronger differential reactions during the second half of acquisition in the PTSD group than in the nTE group. Post-hoc ANOVAS for the CS+ and the CS- indicated heightened reactions both to the CS+ and the CS- in the PTSD group. During extinction, significant Group and CS-type effects were modulated by a Group X CS-type interaction which reflected higher SCRs to the CS+ in the PTSD group than in the nTE group. This was confirmed by the post-hoc ANOVAS which yielded a significant Group effect for the CS+ but not for the CS-.

Valence ratings. During habituation, a significant Group effect was found. Post-hoc ANOVAS indicated that PTSD patients gave more negative valence ratings for both CSs. During acquisition, a significant Group effect pointed to more negative valence ratings in the PTSD group than in the nTE group. Post-hoc analyses showed that this Group effect could be attributed mainly to more negative ratings for the CS- in the PTSD group. Although Figure 1

suggests more negative ratings for the CS+ in PTSD as well, the Group effect in this Post-hoc ANOVA only approached the significance, $F(1, 68)=3.31, p=.078$. During extinction, the Group effect was still significant and could be attributed to more negative ratings for the CS+ in PTSD patients compared to the nTE group.

US-expectancy. No significant Group effects were found during habituation and acquisition. During extinction, the Group effect was significant, which was mainly due to higher US-expectancy ratings for the CS+ in the PTSD group compared to the nTE group.

3.2.3 Comparison of the PTSD group and the TE group

SCR. No between group effects were significant during habituation, acquisition or extinction.

Valence ratings. No effects of the factor Group emerged during habituation and acquisition. During extinction, the Group effect was significant; post-hoc analyses showed that PTSD patients rated the CS+ more negatively than the TE group.

US-expectancy ratings. Interestingly, the Group factor was significant during habituation and extinction, which was due to higher US-expectancy ratings for the CS+ in the PTSD group in contrast to the TE group.

3.2.4 Comparison of the nTE group and the TE group

For SCRs, only the effect of the factor Group during acquisition reached significance which was mainly due to higher SCRs to the CS+ in the TE group than in the nTE group. No other significant between group effects were found.

3.3 Adjustment for pre-acquisition differences: Analysis of Covariance (ANCOVA)

It has been shown that electrodermal responsivity during habituation is positively correlated with differential conditioning effects (Ohman & Bohlin, 1973a, 1973b; Orr et al., 2000). To examine if the heightened electrodermal responsivity found in the PTSD group during

habituation (SCR_{hab} , SCL_{hab}) explains the between group effects observed in the PTSD vs. nTE comparison, they were entered separately as covariates in two Group X CS-type X Time ANCOVAS for acquisition and extinction. The covariate SCL_{hab} was significant, $F(1, 45)=7.793$, $p=.008$, but PTSD still showed significantly heightened responding during acquisition, $F(1, 45)=5.519$, $p=.023$. The same pattern was observed for extinction, effects of SCL_{hab} : $F(1, 45)=4.984$, $p=.031$, Group effect: $F(1, 45)=4.863$, $p=.033$. The covariate SCR_{hab} did not reach significance, and Group effects remained significant in the ANCOVAS for acquisition, $F(1, 45)=8.23$, $p=.006$, and extinction, $F(1, 45)=8.01$, $p=.007$.

Similarly, substantial group differences were present on valence ratings during habituation in the PTSD vs. the nTE group. Analogue to SCRs, habituation ratings were averaged separately for the CS+ and the CS- and entered as covariates into the analyses of acquisition and extinction of this group comparison. The Group effects during acquisition and extinction were not significant after adjusting for these covariates. However, the post-hoc ANCOVA for the CS+ during extinction remained significant after adjustment for its habituation valence ratings, $F(1, 67)=5.06$, $p=.028$.

3.4 Behavioural forced choice test

Figure 2 displays the percentage of participants in each study group choosing the chocolate bar depicting the CS- (i.e. avoiding the CS+) in the three groups. While the nTE group selected equal numbers of both chocolate bars, the PTSD and the TE group significantly deviated from the 50% chance level. They selected the chocolate bar depicting the CS- more frequently (10/23 in the PTSD group, $\chi^2(1)=5.12$, $p=.024$ and 6/18 in the TE group, $\chi^2=6.00$, $p=.014$). Hence, the PTSD and the TE group, but not the nTE group were inclined to show behavioural avoidance.

-----Insert figure 2 about here-----

4 Discussion

We successfully demonstrated differential conditioning on all dependent measures and in all study groups. Consistent with the enhanced conditionability account, we found stronger electrodermal differential conditioning during late acquisition and slowed extinction of the CS+ in the PTSD group compared to the nTE group. This pattern of SCRs corresponds to the findings of Orr et al. (2000) and Peri et al. (2000). It is noteworthy that it was only obtained when contrasting the PTSD group with the nTE group, while the contrast with the TE group was not significant. Peri et al. (2000) who also used traumatised and non-traumatised control groups combined them in the statistical analysis. Hence, one cannot compare our results directly with theirs.

The finding of heightened SCRs to the CS- during acquisition is consistent with the conditioned inhibition account. This indicates that both excitatory (as represented by reactions to the CS+) and inhibitory processes (as represented by reactions to the CS-) are involved in determining the characteristic pattern of conditioned responses in PTSD patients. However, the strong between group effects on electrodermal responding, especially during habituation, point to a generally increased arousal in the PTSD group which affects both CSs. This complicates the interpretation of results with respect to the conditioned inhibition account because general hyperarousal might override associative (inhibitory) effects for single CSs. We will discuss this issue in more detail below.

No support was found for the account of reduced discriminative learning when looking at differential conditioning of SCRs and ratings of valence and US-expectancy. However, the assessment of contingency awareness after the conditioning procedure indicated that PTSD patients had more difficulties in detecting and/or memorizing the stimulus contingencies than the control participants. Ayers, White, and Powell (2003) suggested that general difficulties in learning and memory might be the basis of reduced discrimination learning in PTSD.

Moreover, unaware PTSD patients in our sample tended to have higher BDI-depression scores. Major depression has been associated with deficits in cognitive functioning and verbal memory (Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Fossati et al., 2004).

Unfortunately, the number of unaware participants was too small to further characterize them or to examine their group-specific conditioning patterns. Hence, while the majority of PTSD patients successfully discriminated between the CSs a substantial minority showed signs of impaired discrimination learning.

Evaluative conditioning in PTSD. We extended previous findings by including additional measures from the verbal-cognitive and the behavioural response domain. There was an apparent tendency of PTSD patients to rate the valence of both CSs more negatively throughout all conditioning phases. No differential effects (i.e. CS-type X Group interactions) were found. However, negative valence of the CS+ was most pronounced during extinction in the PTSD group compared to the nTE group, an effect which remained significant even when valence ratings during habituation were statistically controlled. Thus, PTSD patients demonstrated an a-priori tendency to rate both CSs more negative and additionally showed reduced extinction of negative valence, particularly for the CS+. This latter effect is consistent with Michael et al. (submitted), who found delayed extinction of valence ratings of the CS+ in panic disorder compared to healthy controls. Our behavioural avoidance measure underscores these findings: the PTSD group which gave the most negative valence ratings for the CS+ showed higher behavioural avoidance of the CS+ compared to the nTE group. Yet, it is not clear why also the TE group showed this avoidance, since their valence ratings were very similar to those of the nTE group.

Expectancy bias and awareness in PTSD. To our knowledge, this is the first study explicitly assessing US-expectancy ratings during aversive conditioning in PTSD. Most

importantly, we found an overestimation of the probability of the US following CS+ presentations during extinction in PTSD, in contrast to both control groups. Thus, US-expectancy ratings were more sensitive to group differences than SCRs which only differentiated the PTSD and the nTE group. Similar to valence ratings, US-expectancy was already heightened during habituation in contrast to the TE group. Only at the end of acquisition did the three groups give comparable US-expectancy ratings. One could assume that PTSD patients corrected the bias they displayed during habituation due to the experience of the CS+/US contingency, yet it could also be a result of ceiling/floor effects for the CS+/CS- (43.2% of participants gave ratings between 95 and 100 for the CS+ and 50.0% gave ratings of less than 95 for the CS-). Alloy and Tabachnik (1984) proposed that covariation assessments are determined by both the individual's prior beliefs about the contingency and the current situational information regarding the objective contingency between events. Accordingly, we assume that our PTSD patients expressed a general expectancy bias during habituation, which then interacted with conditioning in a confirming manner.

US-expectancy ratings also provided validation of the post-conditioning recognition measure of contingency awareness. Only aware participants gave higher US-expectancy ratings for the CS+ than for the CS-. Continuous measures are considered more sensitive than dichotomous or categorical measures of contingency awareness (Lovibond & Shanks, 2002). The number of unaware participants in our study was relatively high compared to other studies (20.2 % compared to 7.4% in Orr et al., 2000). In contrast to the study by Orr and colleagues, our participants were not informed about the three different stages of the conditioning paradigm. Thus, they were exposed to three contingencies during habituation, acquisition, and extinction. It is conceivable that these rivaling contingencies provided the basis for the expectancy bias and the higher number of unaware individuals in the PTSD group. Yet, real life situations are more complex and involve far more stimulus contingencies than could be realised in this design. It is thus conceivable that these deficits in

discrimination learning (in unaware patients) and expectancy biases (in aware patients) play an important role in the development and maintenance of PTSD.

Methodologically, our findings highlight the importance of incorporating sensitive and reliable measures of contingency awareness into conditioning paradigms especially when studying psychiatric disorders with putative cognitive deficits. Future studies could apply conditioning paradigms involving more than two CSs to study the issue of contingency awareness in more detail.

The role of the CS- in PTSD: failure to respond to safety signals, generalisation, or sensitisation? Compared to the nTE group, PTSD patients demonstrated heightened SCRs to the CS- during acquisition, an effect that was found in three previous conditioning studies in PTSD (Orr et al., 2000, Peri et al., 2000, Grillon & Morgan 1999). Compared to the nTE group, PTSD patients also evaluated the CS- more negatively during habituation and acquisition. According to the *conditioned inhibition* account, this could reflect an inability to inhibit fear in the presence of safety cues. Note however, that these findings can also be interpreted as a *generalization* of the fear response from reinforced (CS+) to non-reinforced stimuli (CS-), because the two CSs were perceptually similar (Mineka & Zinbarg, 2006, Peri et al., 2000). This corresponds well with findings showing that anxiety responses in PTSD are often triggered by stimuli which are perceptually similar to those occurring during the traumatic event (Ehlers, Hackmann, & Michael, 2004).

Apart from such associative processes, the CS- also serves as control stimulus for non-associative processes like *sensitisation* (Ohman, Fredrikson, Hugdahl, & Rimmo, 1976). Accordingly, the presentation of the US alters the experimental context, making it more aversive and arousing, thereby increasing responses to both paired (CS+) and unpaired stimuli (CS-). Assuming that PTSD patients suffer from enhanced sensitivity to threatening contexts (Grillon, 2002b; Grillon & Morgan, 1999; Morgan, Grillon, Southwick, Davis, & Charney,

1995), their reactions to the CS- could reflect augmented sensitization rather than associative effects.

Clinical implications. Delayed extinction in PTSD patients was the most robust finding in our study (see also Orr et al., 2000; Peri et al., 2000; Pitman & Orr, 1986). Extinction of conditioned fear can be viewed as a laboratory analogy for exposure therapy (Bouton, Mineka, & Barlow, 2001; Davey, 1997; Rothbaum & Davis, 2003). The phenomenon of reduced extinction of differential fear reactions indicates that PTSD patients need more time and repetitions to extinguish fear reactions. This is consistent with findings showing that prolonged exposure therapy is effective in PTSD (e.g. Foa et al., 2005).

Not only did PTSD patients demonstrate delayed extinction of psychophysiological responding, they were also slower to extinguish conditioned negative valence in comparison to control participants. These persistent negative evaluations might be relevant for psychotherapy since they have been linked with reinstatement, a laboratory analogue for the return of fear after successful exposure therapy (Rachman, 1989). Reinstatement refers to the re-emergence of conditioned responding after extinction due to unpaired presentations of the US (e.g. Bouton, 1988). Preliminary experimental evidence showed that the negative valence of the CS+ correlated with the magnitude of reinstatement (Hermans et al., 2005).

Moreover, the valence of a CS has been linked to avoidance behaviour. Subtle valence differences (preferences) are thought to guide behaviour especially in situations with low differential response costs (de Houwer et al., 2001; Baeyens, Eelen, & Crombez, 1995). Our behavioural forced choice test represented a situation with low differential response cost, and the results showed that conditioning affected the preferences of the PTSD and the TE group. To illustrate the potential clinical relevance of this point, imagine a PTSD patient who has to choose between two different ways to drive to work, with one of them passing by the street where the traumatic event happened. Exposure therapy (extinction) might have reduced this

patient's fear reactions and negative expectancies with respect to this street. Yet, if subtle conditioned negative valence outlived exposure therapy it might facilitate the avoidance of this street; thereby possibly increasing the chance of relapse. These negative evaluations of conditioned stimuli might be treated with reappraisal procedures or counter-conditioning (Hermans, 2002; Frank, Baeyens, Eelen, Van den Bergh, & Crombez, 1989; but see also de Jong, Vorage, & van den Hout, 2000).

Limitations. Several limitations have to be considered when interpreting the current findings. First, our PTSD group differed from both control groups regarding co-morbid depression which was present in eleven of our PTSD patients but in none of our control participants. However, considering that depression is associated with rather low SCRs (e.g. Iacono et al., 1983), it appears unlikely that the heightened responding in the present study is due to this condition. Yet, the possibility that negative valence ratings or heightened US expectancies might be due to this co-morbid disorder cannot be ruled out.

Second, the usage of several psychoactive medications was reported by the PTSD patients in our study. While some of these agents might depress electrodermal reactions, other might increase them. However, the consistency of our results with findings in non-medicated samples (Orr et al., 2000) makes us confident of the robustness of our findings. More so, it appears unlikely that explicit measures of conditioning (e.g. valence, US-expectancy) were influenced by these medications.

Third, we are not aware of a unitary definition of the degree of psychopathology in traumatized control groups. We allowed for the existence of past psychiatric disorders other than anxiety disorders and required the presence of a trauma fulfilling the A-criterion of the PTSD-diagnosis as a minimum. Still, some participants fulfilled additional symptoms of the DSM-IV diagnosis of PTSD, while not qualifying for the full diagnosis. This might explain why our TE group occupied an intermediate position in some of our results.

Fourth, Lissek et al. (2005) pointed to the failure of differential conditioning designs to adequately account for non-associative processes like sensitisation or reduced habituation when reactions to both CSs are elevated in the patient group. Since this was partially the case in our study, future research designs should add a second procedure with unpaired presentations of the CSs and the US to examine this issue.

Finally, a conceptual limitation of the present study is the use of a cross-sectional design to investigate etiological issues (Kraemer, Yesavage, Taylor, & Kupfer, 2000). Conditioning accounts of PTSD assume to measure a *trait-like* predisposition of individuals to respond stronger to conditioning episodes. Hence, the responses to conditioning protocols obtained in PTSD patients *after* trauma exposure are assumed to reflect their trait-conditionability *before* trauma exposure. Support for this assumption comes from studies showing that conditionability demonstrates considerable heritability (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003), is highly stable over repeated testing (Fredrikson, Annas, Georgiades, Hursti, & Tersman, 1993), and that conditioning is already altered in anxious children (Lieberman, Lipp, Spence, & March, 2005). A first longitudinal study provided preliminary evidence that delayed extinction during fear conditioning before trauma exposure was predictive of PTSD symptoms after trauma exposure (Guthrie & Bryant, 2006). While these findings are generally supportive of the *trait-account* of conditionability, other conceptualisations are possible. Stressful experiences can enhance fear conditioning, possibly by sensitising subjects to subsequent learning (*state-account*). Unsignaled footshocks enhanced subsequent fear conditioning in male rats (Rau, DeCola, & Fanselow, 2005). In humans, a social stressor was found to enhance subsequent differential fear conditioning in male participants (Jackson, Payne, Nadel, & Jacobs, 2006). More longitudinal research is clearly needed to evaluate state and trait accounts of fear conditioning in PTSD.

Conclusions. The result of delayed extinction seems to mirror the course of PTSD, in which the reactions to cues associated with traumatic experiences do not decay over time. Particularly the persistent re-experiencing symptoms seen in PTSD could be explained by this mechanism. In our study, three relatively novel indices of conditioning proved their significance in fear conditioning. The overestimation of aversive outcomes indexed by US-expectancy ratings could be related to the sense of current threat and hypervigilance frequently found in PTSD (Ehlers & Clark, 2000). Likewise, persistent negative evaluations and behavioural avoidance of the CSs could threaten the maintenance of social functioning and behavioural flexibility established by successful exposure therapy.

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Figure Legends

Figure 1: Skin conductance responses (SCR), valence ratings, and US-expectancy ratings for the CS+ and the CS- during habituation, acquisition and extinction in the PTSD group, the TE group and the nTE group

Note. PTSD, Posttraumatic Stress Disorder; TE, trauma-exposed; nTE, non trauma exposed; SCR, Skin conductance reaction; US, Unconditioned stimulus; FIR, first interval response.

Figure 2. Percent avoidance of the chocolate bar depicting the CS+

Note. PTSD, Posttraumatic Stress Disorder; TE, trauma-exposed; nTE, non trauma exposed; CS, conditioned stimulus;

(*), significantly different from 50%, PTSD, $\chi^2(1) = 5.12, p = .024$, TE, $\chi^2 = 6.00, p = .014$.

Table 1. Demographic, psychometric and control measures for the study groups.

	PTSD group M (SD)	Trauma exposed group M (SD)	Non-trauma exposed group M (SD)	Statistic
Age (years)	41.03 (11.10)	40.58 (13.71)	42.18 (8.58)	$F(2, 93)=0.17, p=.84$
Education (years)	41.03 (11.11)	40.58 (13.71)	42.18 (8.58)	$F(2, 90)=0.16, p=.84$
PDS	32.53 (10.13) ^a	9.38 (6.23) ^b	-	$t(1, 49)=9.29, p<.01$
FDS	18.33 (18.40) ^a	7.09 (5.756) ^b	-	$t(1, 39)=4.572, p<.04$
STAI-State	52.47 (10.10) ^a	37.33(10.71) ^b	36.53 (8.38) ^b	$F(2, 91)=27.96, p<.01$
STAI-Trait	57.40 (9.33) ^a	37.92 (10.56) ^b	32.71 (8.81) ^b	$F(2, 91)=63.77, p<.01$
BDI	26.46 (9.51) ^a	6.92 (6.44) ^b	4.53 (4.57) ^b	$F(2, 92)=92.03, p<.01$
US level (mA)	2.26 (1.85) ^a	3.41 (3.01)	3.74 (2.90) ^b	$F(2, 92)=3.12, p=.05$
US rating (-100 to 100)	22.24 (57.87)	21.43 (61.55)	29.76 (55.63)	$F(2, 92)=.20, p=.82$
SCL _{hab} (μS)	8.38 (2.73)	9.93 (6.79)	7.13 (2.51)	$F(2, 62)=2.47, p=.09$
SCR _{hab} (μS)	0.91 (0.30)	1.04 (0.69) ^a	0.70 (0.33) ^b	$F(2, 62)=3.29, p=.04$
UR: SCR (μS)	1.05 (0.45)	1.08 (0.44)	0.82 (0.36)	$F(2, 62)=2.88, p=.06$

Note: PDS, Posttraumatic Diagnostic Scale; STAI-State/Trait, Spielberger State-Trait Anxiety

Inventory; BDI, Beck Depression Inventory; SCL_{hab}, mean skin conductance level at

habituation; SCR_{hab}, mean skin conductance reactions to all stimuli during habituation; US,

unconditioned stimulus; UR, unconditioned response; a, b, c, different superscripts indicate

that groups differed from each other at $p=.05$

Table 2. Selected ANOVA effects for group comparisons on SCRs, and ratings of stimulus valence and US-expectancy

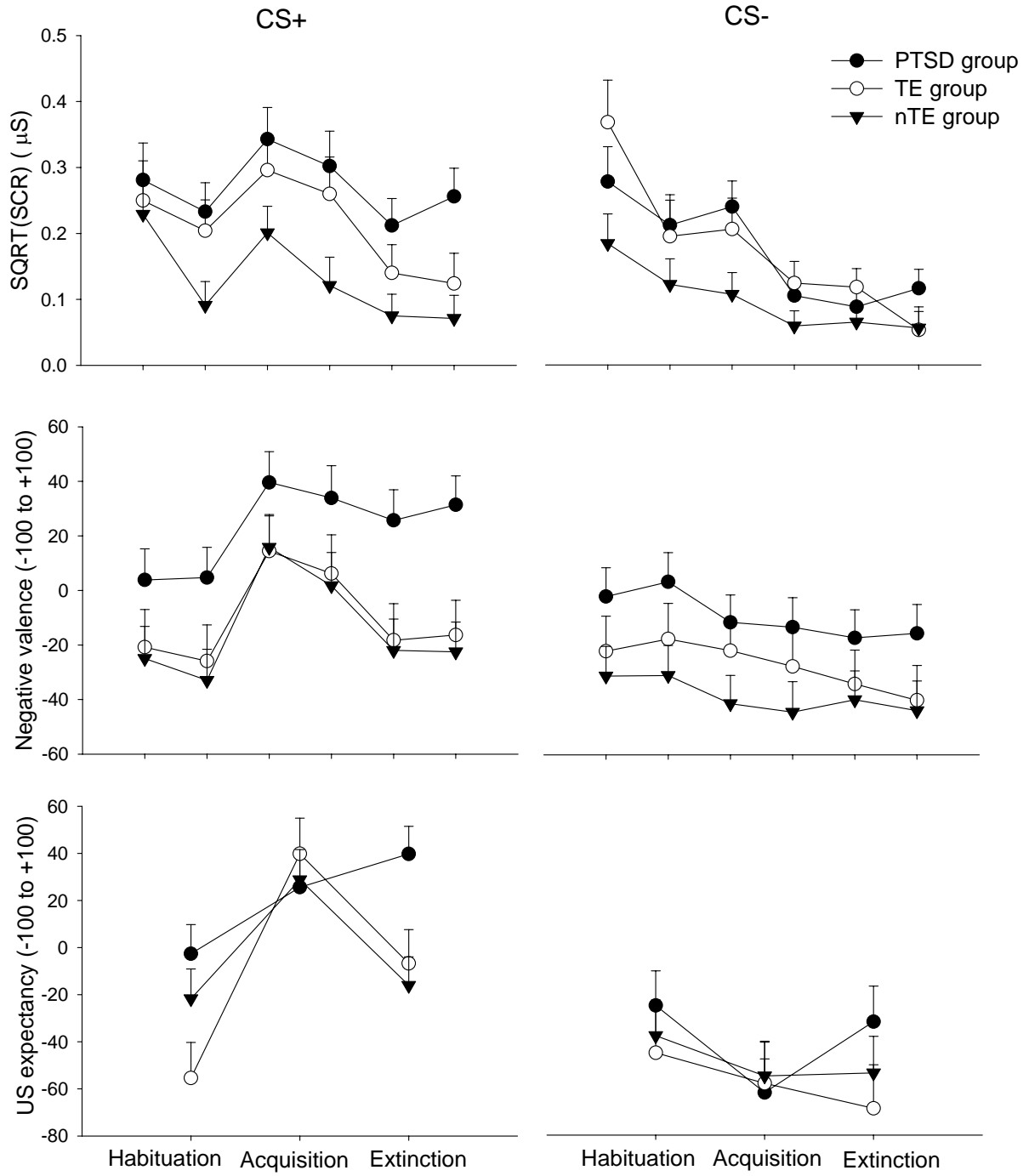
	ANOVA				
	Group	CS-type	Group X CS-type	Post-hoc ^(g)	
				CS-	CS+
	<i>F, p</i>	<i>F, p</i>	<i>F, p</i>	<i>F, p</i>	<i>F, p</i>
PTSD vs. nTE					
<i>SCR</i> ^(a)					
Habituation	Ns	ns	ns	-	-
Acquisition	8.346, .006	26.769, .000	ns	5.796, .020	7.694, .008
Extinction	6.966, .011	12.293, .001	8.050, .007	ns	9.628, .003
<i>Valence</i> ^(d)					
Habituation	7.056, .010	ns	ns	4.899, .030	4.950, .029
Acquisition	6.189, .015	32.933, .000	ns	4.798, .032	ns
Extinction	9.745, .003	15.577, .000	ns	ns	11.077, .001
<i>US-expectancy</i> ^(d)					
Habituation	ns	ns	ns	-	-
Acquisition	ns	35.597, .000	ns	-	-
Extinction	6.480, .013	13.631, .000	ns	ns	10.597, .002
PTSD vs. TE					
<i>SCR</i> ^(b)					
Habituation	Ns	ns	ns	-	-
Acquisition	Ns	25.671, .000	ns	-	-
Extinction	Ns	11.22, .002	ns	-	-
<i>Valence</i> ^(e)					
Habituation	Ns	ns		-	-
Acquisition	Ns	16.811, .000	ns	-	-
Extinction	ns	8.104, .006	ns	-	-
<i>US-expectancy</i> ^(e)					
Habituation	4.851, .032	ns	ns	ns	7.696, .007
Acquisition	ns	30.913, .000	ns	-	-
Extinction	5.590, .021	19.592, .000	ns	ns	6.098, .017
nTE vs. TE					
<i>SCR</i> ^(c)					
Habituation	Ns	ns	ns	-	-
Acquisition	4.29, .044	35.611, .000	ns	ns	4.289, .045
Extinction	Ns	4.949, .031	ns	-	-
<i>Valence</i> ^(f)					
Habituation	ns	ns	ns	-	-
Acquisition	ns	24.033, .000	ns	-	-
Extinction	ns	8.104, .006	ns	-	-
<i>US-expectancy</i> ^(f)					
Habituation	ns	ns	ns	-	-
Acquisition	ns	33.106, .000	ns	-	-
Extinction	ns	7.997, .006	ns	-	-

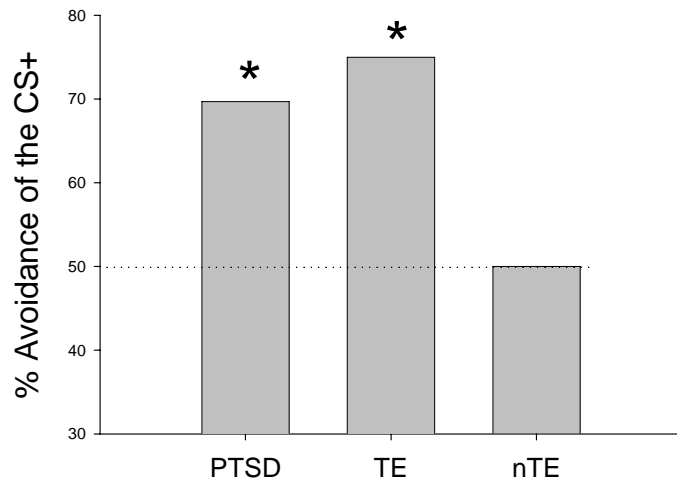
Note. PTSD, posttraumatic stress disorder group; TE, trauma exposed group; nTE = non

trauma-exposed group; SCR, Skin conductance reaction; US expect, US-expectancy ratings;;

(a) F(1, 46); (b) F(1, 35); (c) F(1, 43); (d) F(1, 68); (e) F(1, 58); (f) F(1, 56); (g) Post-hoc tests

were Group (df=1) X Time (df=1) Analyses of Variance





Footnotes

1. Although this is more of a suggestion rather than a formal theory, it is a useful approach to contrast the view of heightened conditionability (S. Lissek, personal communication). In addition, a differential fear conditioning paradigm cannot be expected to produce equally strong inhibitory effects as obtained in studies using A+/AB- procedures (Rescorla, 1969). In the latter, one stimulus is followed by the US (A+ trials), except when accompanied by a second stimulus B (AB- trials, e.g. Chan and Lovibond, 1996). Furthermore, conditioned inhibition of SCRs is typically assessed in a summation test (e.g. Grillon & Ameli, 2001).

2. While eye blink conditioning is also a form of pavlovian discriminative learning it might differ on a number of aspects from the present design, i.e. it is less dependent on contingency awareness (Clark & Squire, 1998)

3. Analyses of second interval responses (time window 4-8 s of the 8 s CS presentation time) were also done, but did not reveal significant between group effects. For ease of reading, all FIR-SCR effects are referred to a SCR effects. The FIR has higher internal consistency and temporal stability compared to the SIR and might therefore better suited for the examination of a potential trait variable like conditionability (Fredrikson et al., 1993). Following Orr et al (2000), we also measured and analyzed heart rate responses and musculus corrugator electromyographic responses (Corrugator-EMG). Heart rate level was higher in the PTSD group compared to both control groups, but contrary to Orr et al., heart rate responses to the CSs and the US were generally lower in PTSD. However, no meaningful conditioning effects (i.e. CS-type-effects) were observed for heart rate or corrugator-EMG, hence these data are not reported. Results are available from the authors on request.