# Verarbeitung emotionaler Reize bei Personen mit einer Zwangsstörung

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# INDEX

## Zusammenfassung

Trotz zahlreicher Untersuchungen lässt sich bei der Zwangsstörung noch kein einheitliches, alle Befunde integrierendes Krankheitsmodell formulieren. Die Verarbeitung von emotionalen Reizen könnte bei Personen mit Zwangsstörungen verändert sein. Dies trägt möglicherweise zur Entwicklung und Aufrechterhaltung der Störung bei. Das Ziel der vorliegenden Arbeit war es, spezifische Komponenten dieser Verarbeitung zu untersuchen. Zuerst wurde in zwei unterschiedlichen Studien überprüft, ob die Orientierung der Aufmerksamkeit zu neuen Reizen bei Patienten mit Zwangsstörungen verstärkt ist. Zu diesem Zweck wurden durch neue Reize evozierte Potentiale im Elektroenzephalogramms (EEG) gemessen. Anschließend wurde in einer Studie überprüft, ob das Verhältnis der Aktivierungen von dem Vermeidungs- zum Annäherungssystem bei den Betroffenen verändert ist. Dies lässt sich an Hand der Ermittlung der hemisphärischen Verteilung von Alpha-Wellen in frontalen Hirnregionen feststellen. Die Ergebnisse der ersten beiden Studien ergaben, dass Patienten unabhängig vom emotionalen Kontext eine stärkere Aufmerksamkeitshinwendung zu neuen Reizen zeigen (Studie 1), was allerdings nicht beobachtet wurde, wenn die neuen Reize innerhalb des Aufmerksamkeitsfokus lagen (Studie 2). Dieses Ergebnis wurde als überaktives Gefahrenerkennungssystem bei Patienten interpretiert. Weiterhin ließ sich feststellen, dass Patienten im Vergleich zu gesunden Kontrollen in frontalen Hirnregionen eine Verlagerung der Alpha Asymmetrie zur linken Gehirnhemisphäre aufwiesen (Studie 3). Dieser Befund wurde unabhängig von einer Stimulierung durch emotionale Reize gemacht. Er lässt sich als stärkere Aktivierung des Vermeidungs- im Verhältnis zum Annäherungssystem deuten. Zusammengefasst zeigte sich bei Patienten mit Zwangsstörungen eine veränderte Verarbeitung von emotionalen Reizen. Diese neurobiologischen Veränderungen lassen sich in das Modell, das der verhaltenstherapeutischen Behandlung der Zwangsstörung zu Grunde liegt, gut integrieren und können es ergänzen. Aus diesen Befunden können auch spezifische Empfehlungen für die Behandlung der Störung abgeleitet werden.

# 1 Einführung

## 1.1 Zwangsstörungen

Bei Zwangsstörungen handelt es sich um psychische Störungen, welche in der Internationalen Klassifikation der Krankheiten (ICD-10; Dilling und Organization (2005)) mit anderen Angststörungen unter den neurotischen-, Belastungs- und somatoformen Störungen gelistet und im Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; Sass, Houben, und Association (1998)) als Angststörung klassifiziert werden. Erkrankte Personen leiden unter sich wiederholenden und aufdrängenden Gedanken, welche bei den Betroffenen als unangenehm erlebt werden (Zwangsgedanken). Die dadurch ausgelösten Anspannungen versuchen sie durch repetitive Handlungen zu reduzieren (Zwangshandlungen).

Die Prävalenz der Störung beträgt ein bis drei Prozent der Bevölkerung (Fontenelle, Mendlowicz, & Versiani, 2006; Ruscio, Stein, Chiu, & Kessler, 2010). Der Verlauf ist oft chronisch (Pinto, Mancebo, Eisen, Pagano, & Rasmussen, 2006) und die Patienten (Eisen et al., 2006) und ihre Angehörigen (Stengler-Wenzke, Kroll, Matschinger & Angermeyer, 2006) berichten über eine niedrigere Lebensqualität. Sowohl eine kognitive Verhaltenstherapie, in deren Verlauf Expositionen mit Reaktionsverhinderung angewendet wurden, als auch eine Pharmakotherapie mit selektiven Serotonin-Wiederaufnahmehemmern waren erfolgreich in der Behandlung von Zwangsstörungen, wobei die Effektivität noch zu steigern ist (Franklin & Foa, 2011).

## 1.2 Modelle der Zwangsstörung

Bei den Ursachen und der Aufrechterhaltung der Zwangsstörung geht man von einem multifaktoriellen Geschehen aus (J. S. Abramowitz, S. Taylor, & D. McKay, 2009). Trotz viel versprechender Ansätze (z.B.: Salkovskis, 1999; Saxena, Brody, Schwartz & Baxter, 1998) lässt sich bislang kein einheitliches, alle Befunde integrierendes Krankheitsmodell der Störung formulieren (J. S. Abramowitz et al., 2009; Karch & Pogarell, 2011). Dies verdeutlicht die Notwendigkeit von weiterführenden Untersuchungen.

Der Behandlung von Zwangsstörungen durch eine kognitive Verhaltenstherapie liegen kognitive Modelle (Rachman, 1997; Salkovskis, 1999, siehe Abbildung 1) handlungsleitend zu Grunde. Nach diesen Theorien treten Gedanken mit zwangsspezifischen Inhalten (z.B. „Habe ich den Herd angelassen?“) auch bei nicht betroffenen Personen auf (Rachman & de

Silva, 1978), sie werden aber von diesen im Unterschied zu Personen mit Zwangsstörungen nicht als bedrohlich verarbeitet. Eine solche Interpretation führt zu einem verstärkten Auftreten der Gedanken und zu dem Versuch, diese zu neutralisieren. Kurzfristig führt das zwar zu einer Abnahme der Angst, langfristig jedoch zu einem verstärkten Auftreten der Gedanken.

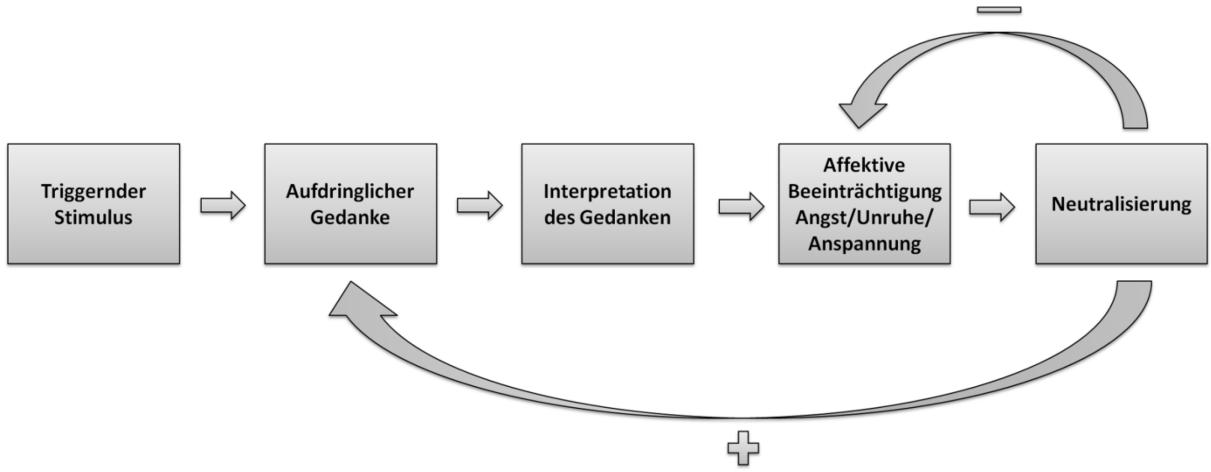


Abbildung 1**:** Ein kognitives Modell für Zwänge (nach Salkovskis, 1999).

Eine Schwäche der genannten kognitiven Modelle ist die fehlende Integration von Vulnerabilitäten, welche nach einem Diathese-Stress-Modell (Chorpita & Barlow, 1998) zur Entstehung der Krankheit beitragen. Durch diese Faktoren ergänzte Modelle wären jedoch darüber hinaus auf Grund der belegten Heredität der Störung (Nicolini, Arnold, Nestadt, Lanzagorta, & Kennedy, 2009) wünschenswert.

Allgemeineren kognitiven Modellen der Angstvulnerabilität und -störungen zufolge (Bishop, 2008; Andrew Mathews & Mackintosh, 1998) spielt eine verstärkte Aufmerksamkeitszuwendung zu emotionalen Reizen bei der Entwicklung und Aufrechterhaltung von Angststörungen eine große Rolle (MacLeod & Mathews, 2012). Diese wurde empirisch bei Personen mit Angststörungen beobachtet (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg & van IJzendoorn, 2007), besonders, wenn die Reize mit einer Gefahr verbunden sind. Sie ist vor allem durch Veränderungen in frühen, unbewussten Verarbeitungsprozessen bedingt (Craske et al., 2009). Dem Modell der kognitiven Vulnerabilität der Angst von Ouimet, Gawronski, und Dozois (2009) folgend, könnten zusätzlich zeitlich spätere Verarbeitungsprozesse der emotionalen Reizverarbeitungen bei Zwangsstörungen verändert sein.

Nach neuroanatomischen Modellen der Zwangsstörung (Aouizerate et al., 2004; Saxena et al., 1998) liegen der Störung veränderte Regelkreisläufe im Gehirn zu Grunde, insbesondere eine veränderte Gehirnaktivität im orbitofrontalen Kortex (OFC), dem anterioren cingulären Kortex (ACC), dem Thalamus, dem Nucleus caudatus und dem dorsolateral frontalen Kortex. Diese Gehirnareale spielen bei der emotionalen Reizverarbeitung eine wichtige Rolle. So scheint beispielsweise im OFC ein integrierendes Zentrum für emotionale Informationsverarbeitung zu liegen (Krawczyk, 2002; Vuilleumier, 2005) und auch der ACC (Bishop, Duncan & Lawrence, 2004; Bush, Luu & Posner, 2000) und der Thalamus (Aouizerate et al., 2004) sind in der emotionalen Verarbeitung involviert. Deswegen lässt sich auch aus diesen Modellen die Annahme entwickeln, dass Zwangsstörungen eine veränderte Verarbeitung von emotionalen Reizen zu Grunde liegt.

Evolutionspsychologische Modelle (Abed & de Pauw, 1998; Brune, 2006; Feygin, Swain, & Leckman, 2006; Gilbert, 2001; Szechtman & Woody, 2004) interpretieren die Symptome der Zwangsstörung im Sinne eines überaktiven Gefahrvermeidungssystems. Aufgrund dieses überaktiven Systems erfolgt eine verstärkte Aufmerksamkeitshinwendung zu Gefahrreizen (Gilbert, 2001).

Zusammenfassend lässt sich hypothetisieren, dass bei Zwangsstörungen Prozesse der emotionalen Reizverarbeitung verändert sind und dass diese zur Entwicklung und Aufrechterhaltung von Zwangsstörungen beitragen.

## 1.3 Die Verarbeitung von emotionalen Reizen bei Zwangsstörungen

Nach der Durchführung mehrerer Studien bei Personen mit Zwangsstörungen spricht die aktuelle Befundlage für eine veränderte emotionale Reizverarbeitung, wobei die Befunde im Vergleich zu anderen Angststörungen weniger eindeutig sind (Craske et al., 2009). Beispielsweise fanden Rao, Arasappa, Reddy, Venkatasubramanian und Reddy (2010) bei Patienten mit Zwangsstörungen im Vergleich zu psychisch gesunden Kontrollpersonen eine erhöhte Aufmerksamkeitshinwendung zu negativen, zwangsrelevanten Reizen, nicht jedoch zu negativen und nicht zwangsrelevanten oder neutralen Reizen. Die Ergebnisse der Studie von Schienle, Schafer, Stark, Walter und Vaitl (2005) zeigen beim Vergleich von angst- bzw. ekelauslösenden Bildern mit neutralen Bildern eine veränderten Gehirnaktivierung bei Patienten mit Zwangsstörungen. Weitere Hinweise auf eine veränderte emotionale Reizverarbeitung liefern die Ergebnisse von Simon, Kaufmann, Musch, Kischkel und Kathmann (2010): Bei Patienten mit Zwangsstörungen wurde während der Verarbeitung sowohl von negativen als auch von zwangsrelevanten Reizen im Vergleich zu neutralen

Reizen eine erhöhte Aktivierung in Gehirnregionen festgestellt, welche mit der Angstentstehung in Verbindung gebracht werden. Schließlich registrierten Harkin, Miellet und Kessler (2012) bei einer Gruppe mit subklinischen Zwangssymptomen eine veränderte Reizverarbeitung, ausschließlich dann, wenn die Aufmerksamkeit auf einen bedrohungsrelevanten Aspekt eines Gegenstandes bezogen war. Andere Studien konnten allerdings keinen Unterschied in der Reizverarbeitung zwischen Patienten mit Zwangsstörungen und gesunden Kontrollpersonen feststellen (Harkness, Harris, Jones & Vaccaro, 2009; Kyrios & Iob, 1998; Moritz, Jacobsen et al., 2004; Moritz & von Muhlenen, 2008).

Modellen der Aufmerksamkeit zur Folge hängt die Aufmerksamkeitshinwendung zu Reizen aber von einem Zusammenspiel automatischer, stimulus geleiteter Bottom-up-Prozesse und Top-down-Kontrollprozesse ab (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Dieses Zusammenwirken wurde in Modellen bezüglich der Hinwendung der Aufmerksamkeit zu bedrohlichen Reizen und hiermit gekoppelt mit Angst (Bishop, 2008; Eysenck, Derakshan, Santos, & Calvo, 2007) und Angststörungen (Clark & Beck, 2011; Andrew Mathews & Mackintosh, 1998) spezifiziert. Die Aufmerksamkeitshinwendung zu potentiell bedrohlichen Reizen nach Andrew Mathews und Mackintosh (1998) hängt beispielsweise von einem automatischen Gefahrerkennungssystem (Bottom-up) und willentlichen Kontrollprozessen (Top-down) ab.

Die verschiedenen Aufmerksamkeitsprozesse ließen sich in den früheren Untersuchungen zur selektiven Aufmerksamkeit bei Patienten mit Zwangsstörungen nicht trennen. So ist nicht auszuschließen, dass spätere Top-down-Prozesse die Ergebnisse von Studien beeinflussen, welche primär automatische Bottom-up-Prozesse messen sollten (Koster, Crombez, Verschuere & De Houwer, 2004; Reinholdt-Dunne, Mogg & Bradley, 2009). Eine unterschiedliche Aktivierung der jeweiligen Prozesse zwischen den verschiedenen Studien könnte somit zu der uneindeutigen Befundlage beigetragen haben.

Eine Trennung der einzelnen Prozesse ist jedoch besonders bei Angststörungen wichtig, da eine Theorie über die Aufmerksamkeit bei Angststörungen (Mogg & Bradley, 1998) von einem Vigilanz-Vermeidungsmuster ausgeht. Danach zeigen Personen mit Angststörungen eine anfänglich verstärkte Aufmerksamkeit in Bezug auf bedrohliche Reize (basierend auf Bottom-up-Prozessen), gefolgt von einer Vermeidung derselben (basierend auf Top-down-Prozessen). Auch könnten andere, spätere Top-Down-Prozesse die Ergebnisse beeinflussen. In der Studie von Cisler & Olatunji (2010) wurde beispielsweise eine

verringerte Loslösung der Aufmerksamkeit von negativen Reizen bei Personen mit stärkerer Angst vor Kontaminierung beobachtet.

Aus diesem Grunde ist es notwendig, einzelne Aufmerksamkeitsprozesse separat zu untersuchen. Hierfür ist das Elektroenzephalogramm (EEG) besonders geeignet, da sich durch seine präzise zeitliche Auflösung (Rösler, 2011) Prozesse der Reizverarbeitung, welche in kurzer Abfolge hintereinander ablaufen, getrennt messen lassen.

## 1.4 Neuigkeitsverarbeitung

Eine schnelle Orientierung zu neuen Reizen dient der Wahrnehmung einer potentiellen Gefahr und stellt vor allem in angstbesetzen oder bedrohlichen Situationen einen adaptiven Überlebensvorteil dar (Garcia-Garcia, Clemente, Dominguez-Borras & Escera, 2010). Als Element unseres biologischen Verteidigungssystems (Bradley, 2009; Garcia-Garcia, Dominguez-Borras, SanMiguel & Escera, 2008) ist diese Orientierung somit Bestandteil der emotionalen Reizverarbeitung.

Die Verarbeitung dieser Reize lässt sich mittels evozierter Potenziale im Elektroenzephalogramms (EEG) messen. Hier wird bei Personen mittels Stimulierung durch neue Reize ein charakteristisches Potential evoziert, welches sich nach ca. 250 bis 300 ms als Positivierung im EEG zeigt. Dieses wird als novelty-P3 bezeichnet und als Maß der Hinwendung von Aufmerksamkeit zu diesen Reizen verwendet (Barry, Macdonald & Rushby, 2010; Courchesne, Hillyard & Galambos, 1975; Friedman, Cycowicz & Gaeta, 2001). Im Unterschied zu anderen Methoden, welche die Orientierung der Aufmerksamkeit (z.B. Stroop-Task) messen, geht man davon aus, dass die novelty-P3 überwiegend die Aktivierung von automatischen, reizgeleiteten Bottom-up-Prozessen der Aufmerksamkeit reflektiert und wenig von zielgeleiteten Top-down-Prozessen beeinflusst wird (Friedman et al., 2001).

Für eine veränderte novelty-P3 bei Patienten mit Zwangsstörungen sprechen Befunde einer erhöhten novelty-P3 bei einer gemischten Patientengruppe mit verschiedenen Angststörungen (Bruder et al., 2002), bei Patienten mit einer posttraumatischen Belastungsstörung (Kimble, Kaloupek, Kaufman & Deldin, 2000) und bei gesunden Kontrollpersonen unter der Androhung eines Elektroschocks (Grillon & Ameli, 1994). Zudem zeigt sich eine teilweise Übereinstimmung der Gehirnregionen, in denen die novelty-P3 generiert wird (Ranganath & Rainer, 2003), mit den Arealen, in welchen Patienten mit Zwangsstörungen eine veränderte Aktivierung zeigen (Menzies et al., 2008) und die in neuroanatomischen Modellen der Zwangsstörung verändert sind.

Eine Studie zur Neuigkeitsverarbeitung bei Patienten mit Zwangsstörungen lag bisher nicht vor.

## 1.5 Annäherung und Vermeidung

Ein weiterer Ansatz zur Messung der Verarbeitung von emotionalen Reizen ergibt sich aus der Theorie von Davidson (1993, 1998). Demnach existieren beim Menschen zwei elementare Systeme, welche verschiedene Formen von Motivation und Gefühlen steuern: ein Annäherungs- und ein Vermeidungssystem. Ersteres motiviert Annäherungsverhalten und generiert Gefühle, welche mit Annäherung verbunden sind (Davidson, 1998). Das Zweite erzeugt negative Gefühle (z.B. Furcht und Ekel), welche mit Rückzug verbunden sind und motiviert Rückzugsverhalten von aversiven Reizen (Davidson, 1998). Für internalisierende psychische Störungen (z.B. Depressionen und Angststörungen) anfällige Personen unterscheiden sich von gesunden Kontrollpersonen darin, dass ihr Vermeidungssystem im Verhältnis zum Annäherungssystem stärker ausgeprägt ist (Davidson, 1993, 1998).

Diese beschriebenen Systeme äußern sich in hemisphärisch spezifischer Aktivität in frontalen Gehirnregionen (Davidson, 1995). So zeigt sich die Mobilisierung des Annäherungssystems in frontal stärker linksseitiger und die des Vermeidungssystems in frontal stärker rechtsseitiger Gehirnaktivität (Davidson, 1998). Diese lässt sich im EEG mittels der inversen Stärke von Alphawellen quantifizieren (Laufs et al., 2003), deren Differenz zwischen den Hemisphären als Alpha Asymmetrie bezeichnet wird. Die Alpha Asymmetrie besteht aus situationsunabhängigen (Trait) und situationsspezifischen Anteilen (State; Hagemann, Hewig, Seifert, Naumann & Bartussek, 2005). Sie lässt sich dementsprechend sowohl während einer Ruhebedingung (z.B. Sitzen mit geschlossenen Augen) als auch unter Reizstimulierung messen. Unter einer Ruhebedingung werden primär die Trait Anteile, bei Stimulierung durch Reize werden zusätzlich die State Anteile der Alpha Asymmetrie gemessen. Außer Videos (Davidson, Ekman, Saron, Senulis & Friesen, 1990) eignen sich auch Bilder zur Stimulierung, um Veränderungen in der Alpha Asymmetrie herbeizuführen (Huster, Stevens, Gerlach & Rist, 2009).

Für eine veränderte Alpha Asymmetrie bei Patienten mit Zwangsstörungen sprechen die Befunde von Studien bei anderen Störungen. Diese belegen die Annahmen von Davidson (1993, 1998) einer stärkeren Aktivierung des Vermeidungs- im Verhältnis zum Annäherungssystem bei depressiven Patienten mit (Bruder et al., 1997) und ohne komorbide Angststörung (Stewart, Coan, Towers & Allen, 2011), bei Patienten mit sozialen Phobien (Davidson, Marshall, Tomarken & Henriques, 2000), mit posttraumatischen

Belastungsstörungen (Rabe, Beauducel, Zollner, Maercker & Karl, 2006) und mit Panikstörungen (Wiedemann et al., 1999). Innerhalb dieser Studien zeigte sich die veränderte Alpha Asymmetrie teilweise nur unter der Stimulierung durch Reize (Davidson et al., 2000; Rabe et al., 2006; Wiedemann et al., 1999) teilweise aber auch zusätzlich unter einer Ruhebedingung (Stewart et al., 2011).

Bei Patienten mit Zwangsstörungen gab es in Studien bisher voneinander abweichende Befunde (Bucci et al., 2004; Kuskowski et al., 1993; Tot, Ozge, Comelekoglu, Yazici & Bal, 2002), welche allerdings methodologische Schwächen aufweisen: bei Kuskowski et al. (1993) handelte es sich um eine zu kleine Stichprobe, bei Bucci et al. (2004) wurden die Eletroden eher zentral angelegt, bei Tot et al. (2002) war die Referenzelektrodenwahl ungeeignet. Aus der unklaren Befundlage und den methodologischen Schwächen früherer Studien ergibt sich der Bedarf weiterer Untersuchungen der Alpha Asymmetrie bei Patienten mit Zwangsstörungen.

## 1.6 Ziel der vorliegenden Arbeit

Das Ziel der vorliegenden Arbeit war es, die Verarbeitung von emotionalen Reizen bei Patienten mit Zwangsstörungen im Vergleich zu gesunden Kontrollpersonen mittels der zwei oben angeführten Ansätze (s.1.4. und 1.5.) – der Neuigkeitsverarbeitung sowie der Aktivität des Annäherungs- und Vermeidungssystem – zu untersuchen. In den ersten beiden Studien wurde die Verarbeitung von neuen Reizen erforscht, in der letzten Studie das Verhältnis zwischen Vermeidungs- und Annäherungssystem.

Im Zentrum der ersten Studie stand die Neuigkeitsverarbeitung bei Patienten mit Zwangsstörungen im Vergleich zu gesunden Kontrollpersonen, wobei die neuen Reize außerhalb des Fokus der Aufmerksamkeit standen. Dabei wurde auch untersucht, ob der Kontext, in dem die neuen Reize auftauchten, einen Einfluss auf deren Verarbeitung hatte. In der zweiten Studie wurde ermittelt, ob sich eine veränderte Verarbeitung von neuen Reizen bei Patienten mit Zwangsstörungen zeigt, wenn diese im Fokus der Aufmerksamkeit stehen. In beiden Studien hypothetisierten wir eine verstärkte Aufmerksamkeitszuwendung zu neuen Reizen bei Patienten mit Zwangsstörungen. In der dritten Studie sollte mittels der Analyse der Alpha Asymmetrie geklärt werden, ob sich das Verhältnis von der Aktivierung des Annäherungs- zur Aktivierung des Vermeidungssystems bei Patienten mit einer Zwangsstörung von dem Verhältnis bei gesunden Kontrollpersonen unterscheidet. Die Hypothese lautete, dass sich bei Patienten mit einer Zwangsstörung im Vergleich zu gesunden

Kontrollpersonen eine stärkere Aktivierung des Vermeidungs- im Verhältnis zu der des Annäherungssystems zeigen würde.

# 2 Zusammenfassung der durchgeführten empirischen Studien

Die in dieser Arbeit durchgeführten drei Studien werden im Folgenden zusammengefasst. Detaillierte Angaben der Methoden und Ergebnisse können in den einzelnen Manuskripten nachgelesen werden.

## 2.1 Verarbeitung neuer Reize außerhalb des Aufmerksamkeitsfokus bei Patienten mit Zwangsstörungen (1. Studie)

In der ersten Studie wurden 21 Patienten mit Zwangsstörungen mit 21 bezüglich des Alters, des Geschlechts und des Bildungsstands vergleichbaren gesunden Kontrollpersonen hinsichtlich ihrer Verarbeitung von neuen Reizen in unterschiedlichen emotionalen Kontexten (negativ, neutral) verglichen. Die Teilnehmer der Studie führten eine visuelle Wiedererkennungsaufgabe durch. Währenddessen hörten sie zwischen der Präsentation von Bildern aufgabenirrelevante Töne, wobei neben einem wiederholten Standardton neue Töne auftraten. Die Patienten zeigten im Vergleich zu den gesunden Kontrollpersonen nach den neuen Tönen eine größere novelty-P3 in ihrem EEG. Dieser Unterschied fand sich vor allem an linksseitigen und zentralen Elektroden (siehe Abbildung 2), sowohl im negativen als auch im neutralen Kontext. Damit wurde deutlich, dass die Unterschiede unabhängig vom Kontext waren, wobei der negative Kontext in keiner Gruppe zu einer signifikant größeren novelty-P3 führte. Die größere novelty-P3 bei Patienten mit Zwangsstörungen lässt sich als verstärkte Orientierungsreaktion auf neue Reize interpretieren. Diese könnte durch eine Hypersensitivität des automatischen reizgeleiteten Aufmerksamkeitssystems hervorgerufen werden, unabhängig von Top-down Prozessen. Hierdurch ist der Befund im Vergleich zu früheren Studien interessant (Foa, Ilai, McCarthy, Shoyer & Murdock, 1993; Lavy, van Oppen & van den Hout, 1994; Rao et al., 2010; Tata, Leibowitz, Prunty, Cameron & Pickering, 1996; Unoki, Kasuga, Matsushima & Ohta, 1999), da diese durch spätere Top-down-Prozesse beeinflusst waren.

Zu diskutieren ist, ob die erhöhte Aufmerksamkeitszuwendung zu neuen Reize im Sinne eines sensibleren Gefahrerkennungssystems gedeutet werden kann, da sich kein Einfluss des Kontextes gezeigt hat. Diese festgestellte Unabhängigkeit der Aufmerksamkeitsorientierung vom emotionalen Kontext unterscheidet sich von Befunden

anderer Studien. Dort zeigte sich bei den gesunden Teilnehmern eine größere novelty-P3 unter Androhung eines Elektroschocks (Grillon & Ameli, 1994) und während der Präsentation von negativen Bildern (Dominguez-Borras et al., 2008; Garcia-Garcia et al., 2008). Die unterschiedlichen Ergebnisse der Studien könnten in dem höheren Ausmaß der gefühlten Bedrohung während des Hörens der neuen Töne in den früheren Studien begründet liegen. So mussten die Versuchspersonen bei Grillon und Ameli (1994) körperliche Schmerzen befürchten. Bei Dominguez-Borras, Garcia-Garcia, und Escera (2008) und (Garcia-Garcia et al., 2008) enhielten die Auswahl der negativen Bilder Darstellungen mit explizit sichtbaren Verwundungen, gleichzeitig wurden die neuen Töne während der Präsentation der Bilder eingespielt. Bei Grillon und Ameli (1994) zeigte sich eine größere novelty-P3 unter Androhung eines Elektroschocks nur bei passiver Wahrnehmung neuer Reize. Ein Grund könnte sein, dass das Gefahrerkennungssystem besonders auf unerwartete neue Reize außerhalb des Aufmerksamkeitsfokus reagiert, da diese potentiell gefährlicher sind. Ob Patienten mit Zwangsstörungen generell eine stärkere Orientierung zu neuen Reizen zeigen, oder dies nur dann auftritt, wenn die neuen Reize passiv wahrgenommen werden, sollte in der zweiten Studie untersucht werden.

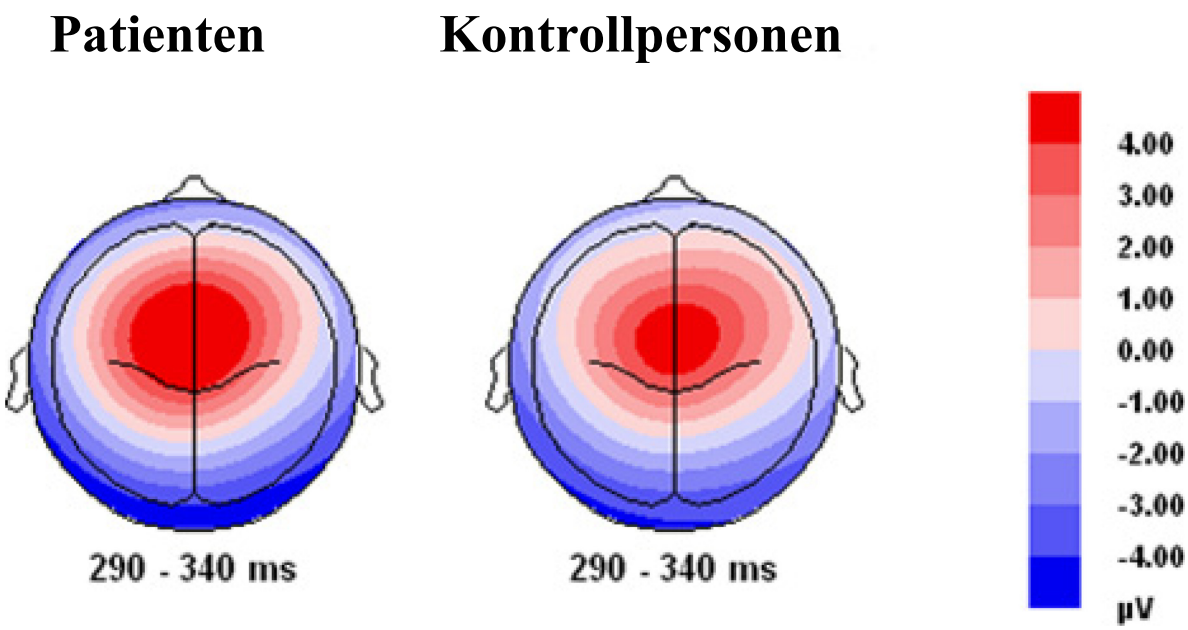


Abbildung 2**:** Topographische Verteilung (Gleichabständige 90° Darstellung) des ereignis-korrelierten evozierten Potenzials nach neuen Reizen (novelty-P3) bei Patienten und Kontrollpersonen.

## 2.2 Verarbeitung neuer Reize innerhalb des Aufmerksamkeitsfokus bei Patienten mit Zwangsstörungen (2. Studie)

In der zweiten Studie wurde erneut die Hinwendung von Aufmerksamkeit zu neuen Reizen bei Patienten mit Zwangsstörungen mit der bei gesunden Kontrollpersonen verglichen. Im Unterschied zur ersten Studie führten die Versuchspersonen statt einer visuellen Wiedererkennungs- eine „Novelty Oddball“ Aufgabe durch. Dabei hörten die Studienteilnehmer in einer pseudo-randomisierten Reihenfolge einen sich wiederholenden Standardton (76%), einen sich wiederholenden Zielton (12%) und unterschiedliche neue Töne (12%). Per Knopfdruck sollten die Teilnehmer so genau und so schnell wie möglich auf den Zielton reagieren. Im Vergleich zur ersten Studie waren die neuen Reize damit direkter in die Aufgabenstellung eingebettet und somit stärker in den Aufmerksamkeitsfokus gestellt. Des Weiteren gab es im Unterschied zur ersten Studie keine Manipulation des Kontextes, welcher neutral gehalten wurde. Ziel war es, zu untersuchen, ob sich auch in dieser Aufgabenstellung ein Unterschied zwischen Patienten mit Zwangsstörungen und gesunden Kontrollpersonen bei der Verarbeitung von neuen Reizen zeigen würden. Im Ergebnis fanden sich keine signifikanten Unterschiede in der novelty-P3 zwischen den 20 Patienten mit Zwangsstörungen und den 20 gesunden Kontrollpersonen. Gründe für die unterschiedlichen Ergebnisse der ersten und der zweiten Studie könnten darin liegen, dass die neuen Reize in der ersten Studie außerhalb des Fokus der Aufgabenstellung lagen. So mussten in der zweiten Studie die Töne mit dem Zielton abgeglichen werden. Für diese Interpretation sprechen die Befunde von Grillon und Ameli (1994) einer erhöhten novelty-P3 unter der Androhung eines Elektroschocks nur in einem passiven und nicht in einem aktiven Aufmerksamkeitsmodus. Dies zu überprüfen bedarf einer weiteren Studie, in der die novelty-P3 bei Patienten mit Zwangsstörungen sowohl in einem aktiven als auch in einem passiven Aufmerksamkeitsmodus mit gesunden Kontrollpersonen verglichen wird. Diese Spezifität der veränderten Reizverarbeitung könnte an einer unterschiedlich starken Aktivierung des Gefahrerkennungssystems in den beiden Bedingungen liegen und auch dazu beitragen, dass die Befundlage zur emotionalen Reizverarbeitung im Vergleich zu anderen Angststörungen weniger eindeutig ist (Craske et al., 2009).

## 2.3 Annäherungs- und Vermeidungssystem bei Patienten mit Zwangsstörungen (3. Studie)

In der dritten Studie wurde die Alpha Asymmetrie bei 18 Patienten mit Zwangsstörungen mit der von 18 bezüglich des Alters, des Geschlechts und des

Bildungsstands vergleichbaren gesunden Kontrollpersonen verglichen. Hierbei wurde die Alpha Asymmetrie während einer sechsminütigen Ruhephase und während des Betrachtens von neutralen, negativen und zwangsrelevanten Bildern gemessen. Die Teilnehmer der Studie hatten die Aufgabe, sich während der Ruhephasen auf ein Fixationskreuz und während der Präsentation der Bilder auf diese zu fixieren. Die Patienten mit Zwangsstörungen zeigten eine Verlagerung der Alpha Asymmetrie zur linken Gehirnhemisphäre in allen Bedingungen (siehe Abbildung 3).

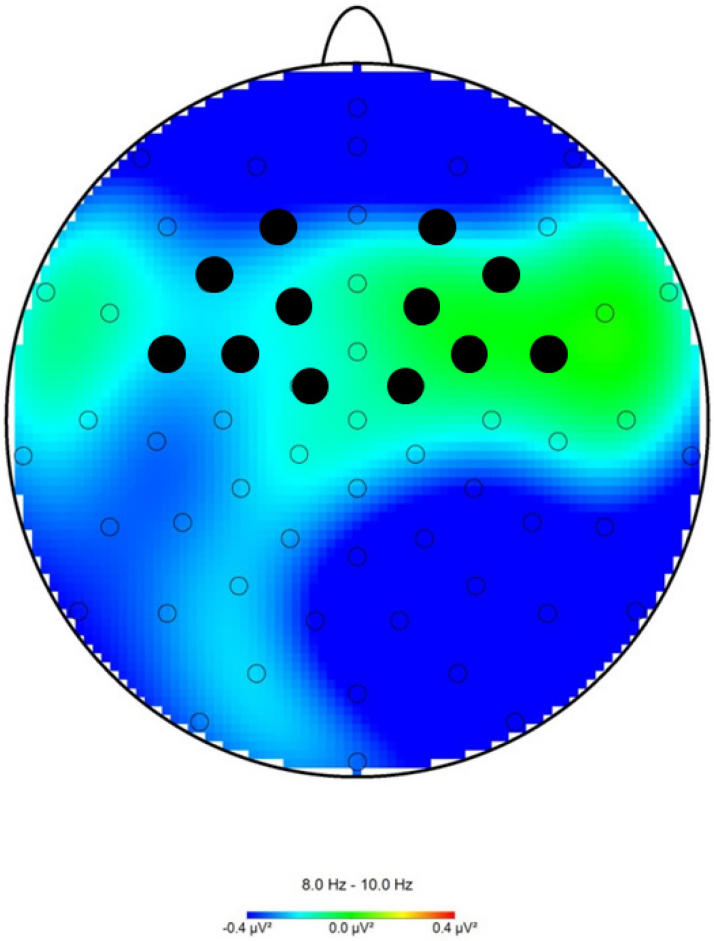


Abbildung 3**:** Topographische Verteilung (Gleichabständige 90° Darstellung) der Differenz der unteren Alphaaktivität (8-10 Hz) von Kontrollpersonen und Patienten mit Zwangsstörungen über alle Bedingungen hinweg. Die in den Rechnungen verwendeten Elektroden sind markiert.

Der Unterschied zwischen den Versuchspersonengruppen blieb auch bei dem Betrachten von negativen Bildern bestehen, was bei beiden Gruppen im Vergleich zu den anderen Bedingungen zu einer Verlagerung der Alpha Asymmetrie zur linken Gehirnhemisphäre führte. Die Veränderungen waren für das untere Alphaband (8-10 Hz) und für die frontalen Elektroden spezifisch. Die divergente Alpha Asymmetrie bei Patienten mit Zwangsstörungen kann als erhöhte Aktivität ihres Vermeidungs- im Verhältnis zum Annäherungssystem interpretiert werden. Es zeigte sich, dass sich dieses Ergebnis nicht auf ein einzelnes System zurückführen ließ, sondern aus dem Zusammenspiel beider Systeme verstanden werden muss. Die andersartige Alpha Asymmetrie entspricht den Befunden bei anderen Patientengruppen (Davidson et al., 2000; Rabe et al., 2006; Stewart et al., 2011; Wiedemann et al., 1999). Aufgrund ihrer Unabhängigkeit vom emotionalen Kontext zeigte die Alpha Asymmetrie bei Patienten mit Zwangsstörungen eine größere Ähnlichkeit zur Alpha Asymmetrie bei depressiven Patienten (Stewart et al., 2011) als bei Patienten, die unter andere Angststörungen leiden (Davidson et al., 2000; Rabe et al., 2006; Wiedemann et al., 1999).

# 3 Zusammenfassende Diskussion

Fasst man die Ergebnisse der drei Studien zusammen, so unterscheiden sich Patienten mit Zwangsstörungen von gesunden Kontrollpersonen bei der Verarbeitung von emotionalen Reizen in folgender Hinsicht: Patienten mit Zwangsstörungen reagierten verstärkt auf neue Reize, allerdings nur dann, wenn diese nicht im Fokus der Aufmerksamkeit lagen (Studien 1 und 2). Des Weiteren zeigten die Patienten eine verstärkte Aktivität des Vermeidungssystems im Verhältnis zur Aktivität des Annäherungssystems (Studie 3).

Hiermit ergänzen sie die Befundlage zur Verarbeitung von emotionalen Reizen bei Patienten mit Zwangsstörungen (Craske et al., 2009) und stehen in Übereinstimmung mit früheren Studien einer veränderten Verarbeitung (Harkin et al., 2012; Rao et al., 2010; Schienle et al., 2005; Simon et al., 2010). Die Resultate der dritten Studie zeigten, dass die Unterschiede teilweise global auftreten. Der Vergleich der ersten und zweiten Studie zeigte, dass die Ergebnisse teilweise auch kontextspezifisch sind. Die Kontextspezifität der veränderten Aufmerksamkeit könnte dazu beitragen, dass deren Befundlage bei Patienten mit Zwangsstörungen bisher weniger eindeutig ist als bei anderen Angststörungen (Craske et al., 2009).

Die verstärkte Reaktion auf neue Reize bei Patienten mit Zwangsstörung kann als Orientierungsreaktion zu neuen Reizen verstanden werden, welche als Teil unseres biologischen Verteidigungssystem im Sinne eines Gefahrerkennungssystems (Bradley, 2009;

Garcia-Garcia et al., 2008) dient. Die fehlende Kontextspezifität innerhalb der ersten Studie spricht jedoch gegen diese Hypothese.

Theoretisch könnte eine erhöhte Aufmerksamkeitszuwendung zu neuen Reizen auch durch ein stärkeres Neugierverhalten („sensation seeking“) erklärt werden. Bei Patienten mit Zwangsstörungen ist dies jedoch unwahrscheinlich, da ihr Temperament durch ein niedriges Neugierverhalten und eine größere Schadensvermeidung gekennzeichnet ist (Alonso et al., 2008). Um mögliche Zusammenhänge zu eruieren bietet sich die experimentelle Untersuchung mittels einer Studie an, die sowohl die novelty-P3 als auch das Temperament der Patienten misst. Für die Interpretation eines Gefahrerkennungssystems spricht darüber hinaus, dass Patienten mit Zwangsstörungen sich zu neuen Reizen nur dann stärker als Kontrollpersonen orientierten, wenn die Reize passiv wahrgenommen wurden. Denn im Sinne eines Gefahrerkennungssystems ist es am entscheidendsten, Gefahren schnell wahrzunehmen, wenn die Aufmerksamkeit auf Anderes fokussiert ist.

Die Patienten mit Zwangsstörungen unterschieden sich auch in einem weiteren Gebiet der Verarbeitung von emotionalen Reizen, da sie eine von gesunden Kontrollpersonen abweichende Alpha Asymmetrie zeigten. Die Ergebnisse können nach Davidson (1998) als eine stärkere Aktivierung des Vermeidungssystems im Verhältnis zur Aktivierung des Annäherungssystems interpretiert werden. Zu betonen ist, dass die Aktivität des Vermeidungssystems prinzipiell evolutionär sinnvoll ist. Nach Davidson (1998) könnte eine Überaktivierung dieses Systems gegenüber der Aktivierung des Annäherungssystems eine bedeutsame Rolle bei der Entstehung und Aufrechterhaltung von internalisierenden Störungen, d. h. auch der Zwangsstörungen, spielen. Grund hierfür könnte sein, dass die veränderte Aktivierung zu einer schlechteren emotionalen Regulierung führt. So stellten Jackson et al. (2003) fest, dass eine stärkere Aktivierung des Vermeidungssystems im Verhältnis zum Annäherungssystems mit einem gesteigerten Augenblinken als Reaktion auf einen lauten Ton nach der Präsentation eines negativen Bildes positiv korrelierte.

Die größere Aktivität des Vermeidungs- gegenüber des Annäherungssystems könnte auch mit bedingen, dass Patienten mit Zwangsstörungen über eine vermehrte Anzahl von depressiven Symptomen berichten (Moritz, Meier, Hand, Schick & Jahn, 2004), was sich auch in einer höheren Komorbidität von depressiven Störungen zeigt (Ruscio et al., 2010). Schließlich könnte sie auch zu einer Vielzahl anderer neuropsychologischer Veränderungen bei betroffenen Personen beitragen. Hiermit ließe sich beispielsweise erklären, dass Patienten mit Zwangsstörungen ein schnelleres Vermeidungslernen zeigen und sich weniger positiven Stimuli nähern (Endrass, Kloft, Kaufmann & Kathmann, 2011).

Geht man von einer Überaktivierung dieses evolutionär sinnvollen Gefahrerkennungssystems bei Patienten mit Zwangsstörungen aus, könnte diese zur Entwicklung und Aufrechterhaltung der Störung beitragen. Auch eine aufgrund der verstärkten Aktivierung des Vermeidungssystems schlechtere emotionale Regulierung könnte hierbei eine Rolle spielen, da die Patienten dadurch potenziell weniger in der Lage sind, mit stressreichen, emotionalen Situationen umzugehen.

Diese Hypothesen werden durch die Einordnung der Befunde der Studien in das kognitive Modell der Zwangsstörung nach Salkovskis (1999) klarer (siehe Abbildung 4). Hierbei würde das Gefahrerkennungssystem auf Grund seiner Überaktivierung (Studien 1 und 2) bereits von leicht bedrohlichen Reizen intensiv angeregt. Dies könnte zum einen dazu führen, dass aufdringliche Gedanken häufiger auftauchen. Zum anderen könnte die stärkere Aktivierung der entsprechenden Gehirnareale darin resultieren, dass diese Reize auch als bedeutsamer bewertet werden. Die erhöhte Aktivität des Vermeidungssystems im Verhältnis zur Aktivität des Annäherungssystems (Studie 3) könnte sich erstens darin auswirken, dass die affektive Beeinträchtigung stärker ausfällt. Zweitens könnte sie dazu beitragen, dass Patienten mit Zwangsstörungen die durch die Gedanken entstandene Unruhe schlechter regulieren können und infolgedessen dysfunktionale Verhaltensweisen wie Vermeidung, Wegdrängen der Gedanken und Neutralisierung durch Zwangshandlungen zeigen. Diese Verhaltensmuster erhalten die Störung aufrecht, da es durch sie zu keiner Falsifizierung der dysfunktionalen Kognitionen kommt. So betrachtet könnten diese krankheitsaufrechterhaltenden Verhaltensweisen indirekt durch eine größere Aktivität des Vermeidungssystems verstärkt werden. Als Vulnerabilität verstanden könnten die in den Studien gefundenen psychobiologischen Veränderungen bei Zwangsstörung somit zur Entwicklung und Aufrechterhaltung der Störung beitragen

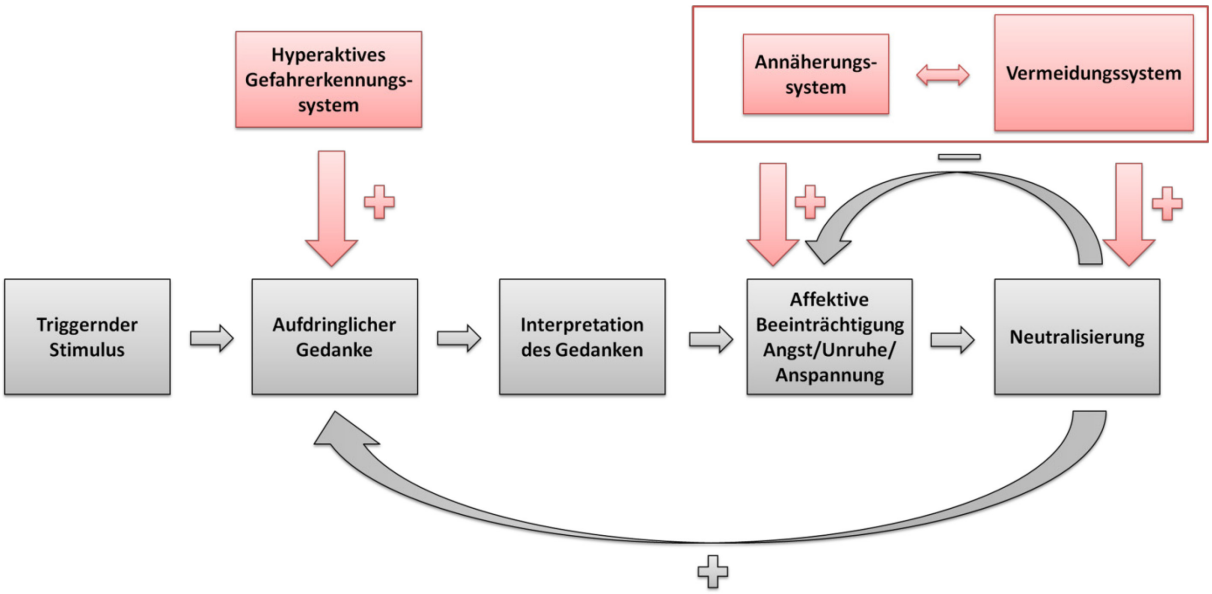


Abbildung 4**:** Integration der Studienergebnisse in ein kognitives Modell für Zwänge nach (Salkovskis, 1999).

Sollten ein aktiveres Gefahrenerkennungs- und ein aktiveres Vermeidungssystem (im Verhältnis zum Annäherungssystem) für die Entstehung von Zwangsstörungen mit verantwortlich sein, ließe sich hiermit auch erklären, warum die Krankheit oft durch Stress ausgelöst wird (Coles, Johnson & Schubert, 2011). Nach dem Modell von A. Mathews und MacLeod (2002) ist ein Gefahrerkennungssystem bei erhöhtem Stress generell aktiver. Darüber hinaus könnten Personen unter Stress tendenziell ein stärker aktiviertes Vermeidungssystem zeigen, um weitere Belastungen zu vermeiden. Ein aktiveres Gefahrerkennungssystem könnte auch die klinisch beobachtbare Hypervigilanz bei Patienten mit Zwangsstörungen erklären.

Meines Wissens liegt bisher keine Studie vor, in der die Zusammenhänge zwischen dem Verhältnis der Aktivierung des Vermeidungssystems zu der des Annäherungssystems und der Zuwendung von Aufmerksamkeit zu neuen Reizen untersucht wurden. Denkbar wäre, dass den bei Zwangsstörungen gefundenen Veränderungen der emotionalen Reizverarbeitung die gleiche Vulnerabilität zu Grunde liegt. So kann man hypothetisieren, dass diese auf einen allgemeinen Faktor zurückzuführen sind. Allerdings werden Unterschiede zwischen den beiden untersuchten emotionalen Reizverarbeitungen deutlich, wenn man diese Ergebnisse mit Studien zur emotionalen Reizverarbeitung bei Patienten mit anderen Störungsbildern vergleicht. Die Aktivität des Gefahrerkennungssystems ist bei Patienten mit anderen Angststörungen ebenso erhöht (Bruder et al., 2002; Kimble et al., 2000) bei Patienten mit

Depressionen jedoch verringert (Bruder et al., 2009; lv, Zhao, Gong, Chen & Miao, 2010). Die Kontextunabhängigkeit einer stärkeren Aktivierung des Vermeidungssystems im Verhältnis zur Aktivierung des Annäherungssystems zeigt sich bei depressiven Patienten (Stewart et al., 2011) und ist bei Patienten mit anderen Angststörungen eher kontextabhängig (Davidson et al., 2000; Rabe et al., 2006; Wiedemann et al., 1999).

Zusammengefasst scheint die emotionale Reizverarbeitung von Patienten mit Zwangsstörungen Überschneidungen mit der von Patienten mit depressiven Störungen (Alpha Asymmetrie) und Patienten mit anderen Angststörungen (novelty-P3) aufzuweisen. Die Unterschiede beider emotionaler Reizverarbeitungen zwischen Patienten mit verschiedenen Störungen können demzufolge eher dafür zu sprechen, dass beide emotionale Reizverarbeitungen nicht auf einem gemeinsamen Faktor basieren. Dies entspricht einem multifaktoriellen Konzept der Entstehung und Aufrechterhaltung der Störung. Zur Festigung dieser Annahme ist die Durchführung weiterer Studien notwendig, innerhalb derer eine Patientengruppe mit Zwangsstörungen sowohl mit einer Patientengruppe mit anderen Angststörungen als auch mit einer Patientengruppe mit depressiven Störungen verglichen wird.

Die Gegenüberstellung mit anderen Studien lässt sich in die allgemeine Diskussion der kategorialen Einordnung der Zwangsstörung im Rahmen der Neukonzeptualisierung des DSM eingliedern. Da es sowohl Überschneidungen als auch Unterschiede im Vergleich der emotionalen Reizverarbeitung von Patienten mit Zwangsstörungen und Patienten mit Angststörungen gibt, wird die Empfehlung von Stein et al. (2010) und Phillips et al. (2010) gestützt, die Zwangsstörung weiterhin innerhalb der Angststörungen mit der veränderten Bezeichnung „Störungen aus dem Angst- und Zwangsspektrum“ zu klassifizieren. Es sollte ihnen jedoch eine gesonderte Unterkategorie von Störungen im Zwangsspektrum zugewiesen werden. In diesem Zusammenhang ist auch bemerkenswert, dass Patienten mit Zwangsstörungen eine hohe Komorbidität mit anderen Angststörungen sowie mit depressiven Störungen zeigen (Ruscio et al., 2010).

Innerhalb der veränderten emotionalen Reizverarbeitungen bei Patienten mit Zwangsstörungen ließ sich eine Gemeinsamkeit feststellen: In den Studien eins und drei zeigte sich die veränderte emotionale Reizverarbeitung unabhängig vom emotionalen Kontext. Dies könnte auf die generelle Inflexibilität von Patienten mit Zwangsstörungen zurückzuführen sein, sich an neue Situationen anzupassen. Das Muster zeigt sich bei ihnen auch in anderen Bereichen. So fanden Wetterneck et al. (2011) einen Zusammenhang zwischen der Persönlichkeitseigenschaft einer geringen Flexibilität und der Schwere der

Störung. Endrass et al. (2010) konnten bei Patienten im Gegensatz zu gesunden Kontrollpersonen keinen Unterschied der eigenen Erfolgskontrolle zwischen einer neutralen und einer Bestrafungsbedingung feststellen. Diese Inflexibilität hinsichtlich der Anpassung an die aktuelle Situation könnte auch zur Entwicklung und Aufrechterhaltung der Störung beitragen, indem Patienten nicht ausreichend zwischen potenziell stark bedrohlichen und schwach bedrohlichen Situationen unterscheiden. Eine durch ein hohes Maß an Inflexibilität gekennzeichnet Persönlichkeitsstörung ist die anankastische Persönlichkeitsstörung. Es lässt sich hypothetisieren, dass die Inflexibilität eine Folge oder Ursache dafür sein könnte, dass bei Patienten mit Zwangsstörungen eine hohe Rate an komorbider anankastischer Persönlichkeitsstörung festgestellt wurde (Friborg, Martinussen, Kaiser, Overgard, & Rosenvinge, 2013). Dies ist von besonderem Interesse, da Patienten mit Zwangsstörung, welche zusätzlich an einer komorbiden anankastischen Persönlichkeitsstörung erkrankt sind, weniger von einer Expositionsbehandlung mit Reaktionsverhinderung profitieren (Pinto, Liebowitz, Foa & Simpson, 2011). Darüber hinaus tritt auch bei Verwandten von Patienten mit Zwangsstörungen eine erhöhte Rate an anankastischen Persönlichkeitsstörungen auf (Samuels et al., 2000). Um einen Zusammenhang zwischen der Inflexibilität und der anankastischen Persönlichkeitsstörung zu überprüfen, sollte diese Persönlichkeitsdimension bei zukünftigen Untersuchungen mit einbezogen werden. Eine Analyse der Inflexibilität von Verwandten der Patienten mit Zwangsstörungen in neurobiologischen Studien wäre ebenfalls wünschenswert. Bezüglich des Gefahrerkennungssystems bedarf die Interpretation einer Inflexibilität jedoch noch weiterer Klärung, da in der ersten Studie auch bei den gesunden Kontrollpersonen kein Kontextunterschied ermittelt wurde.

Ungeklärt ist, inwiefern die geänderten emotionalen Reizverarbeitungen bei den Patienten schon vor der Störung bestanden haben oder erst nach deren Ausbruch auftraten. Um dies zu analysieren, müssten Risikogruppenstudien durchgeführt werden. Zusätzlich wäre es erstrebenswert zu klären, ob die Veränderungen durch eine Behandlung zurückgehen oder weiter bestehen. In einer dichotischen Höraufgabe zeigte sich bei Foa und McNally (1986), dass Patienten mit einer Zwangsstörung zwangsrelevante Wörter sensitiver wahrnahmen als auf neutrale. Nach einer Verhaltenstherapie zeigte sich kein Unterschied mehr. Insgesamt ergibt sich bisher bezüglich der Modifikation von kognitiven Funktionen bei Patienten mit Zwangsstörungen durch Behandlungen ein gemischtes Bild (Vandborg et al., 2012). Fraglich bleibt, ob die Modifikation nach einer Therapie dauerhaft ist oder ob die dysfunktionalen kognitiven Funktionen durch Stress wieder auftauchen.

Es wäre darüber hinaus wünschenswert, die Studien mit Hilfe von größeren Stichproben zu replizieren. Vor dem Hintergrund der Heterogenität der Zwangsstörung (Leckman et al., 2010; Mataix-Cols, Rosario-Campos, & Leckman, 2005) und der hierdurch möglichen Subtypisierung auf neurobiologischer Ebene wäre eine Kombination beider und/oder das Einbeziehen weiterer neurobiologische Vorgänge wichtig. In Kombination mit anderen Befunden könnten spezifische neurobiologische Unterschiede zwischen den Patienten bei der Zuordnung zu bestimmten Therapieverfahren helfen. Dabei würde man primär untersuchen, ob die Patienten besser auf eine Pharmakotherapie oder auf eine Psychotherapie ansprechen, oder ob eine Kombination von beiden sinnvoll wäre. Bezüglich der Aktivität der Alphawellen lassen sich hierfür aufschlussreiche Befunde anführen. So zeigte sich bei Patienten mit depressiven Störungen, die durch eine psychopharmakologische Behandlung Besserungen zeigten, eine stärkere Alphaaktivität auf der rechten als auf der linken Hemisphäre (Bruder et al., 2001). Patienten, welche durch eine psychotherapeutische Behandlung ansprachen, zeigten ein entgegengesetztes Muster der Alphaaktivität (Deldin & Chiu, 2005). Patienten mit Zwangsstörungen, welche auf eine psychopharmakologische Behandlung reagieren, wiesen generell erhöhte Alphawerte auf (Prichep et al., 1993). Diese ersten vielversprechenden Befunde sollten ausgebaut werden.

Wenn ein überaktives Gefahrerkennungssystem und eine verstärkte Aktivität des Vermeidungs- im Verhältnis zum Annäherungssystem zur Entstehung und/oder Aufrechterhaltung von Zwangsstörungen beitragen würde, wäre dies nicht nur für die Zuordnung zu unterschiedlichen Therapieverfahren, sondern auch generell für die Behandlung der Störung von Bedeutung. Hier soll insbesondere auf psychotherapeutische Verfahren eingegangen werden. Zwar sind diese mittels einer kognitiven Verhaltenstherapie bei Einzeltherapien (Franklin & Foa, 2011; Rosa-Alcazar, Sanchez-Meca, Gomez-Conesa, & Marin-Martinez, 2008; Whittal, Thordarson, & McLean, 2005), unter Einbeziehung der Partner (Abramowitz et al., 2013) oder als Gruppentherapie erfolgreich (Jonsson & Hougaard, 2009). Allerdings zeigten sich bei diesen Therapieformen hohe Abbruchraten (dropouts) von bis zu 30% (Abramowitz, 2006; Jonathan S. Abramowitz, Steven Taylor, & Dean McKay, 2009). Zusätzlich konnten von den Patienten, welche bis zum Ende der Sitzungen teilnahmen, 20% nicht von ihnen profitieren (Abramowitz, 2006). Hieraus ergibt sich die Notwendigkeit von Verbesserungen der kognitiven Verhaltenstherapie, indem diese beispielsweise durch weitere psychotherapeutische Methoden ergänzt wird. Bezogen auf die Ergebnisse der Studien könnte es erfolgversprechend sein, die emotionale Reizverarbeitung stärker mit einzubeziehen. Hierbei lassen sich zum einen Behandlungsstrategien entwickeln, welche die

Aufmerksamkeitszuwendung direkt beeinflussen, und zum anderen solche, welche die Bewertung der emotionalen Aktivierung verändern (Taylor & Liberzon, 2007). Bezüglich der erstgenannten könnte eine Aufmerksamkeitsbias-Veränderungs-Methode erfolgversprechend sein, welche bei ängstlichen gesunden Personen sowie bei Patienten mit einer generalisierten Angststörung zu einer Reduktion der Ängstlichkeit führte (Hakamata et al., 2010). Entsprechend der zweitgenannten zeigte sich die Akzeptanz- und Commitment Therapie, die eine Akzeptanz von Emotionen implementiert, in einer Studie bei der Behandlung von Zwangsstörungen mit einer niedrigeren Abbruchrate von 10% als erfolgreich (Twohig, Hayes, & Masuda, 2006). Eine gleichzeitig reduzierte depressive Symptomatik ist insbesondere aufgrund einer Verschlechterung der Behandlungsergebnisse durch eine komorbide Depression (Abramowitz, 2006) von Interesse. Bei allen therapeutischen Methoden bleibt fraglich, ob sie frühe Aufmerksamkeitsprozesse verändern oder nur spätere Aufmerksamkeitsprozesse beeinflussen (Browning, Holmes, & Harmer, 2010), wobei eine Veränderung späterer Aufmerksamkeitsprozesse auch zu einer Änderung von frühen Aufmerksamkeitsprozessen führen kann (Mansell, 2000). Auch für eine Steigerung der Aktivität des Annäherungssystems im Verhältnis zum Vermeidungssystem waren spezifische Interventionen erfolgreich. So führte Achtsamkeitsmeditation zu dieser Steigerung (Davidson et al., 2003). Diese ist in der Mindfulness-based cognitive therapy (MBCT) aufgenommen, welche bei Patienten mit einer depressiven Episode in der Vergangenheit zu gleichen Effekten führte (Barnhofer et al., 2007). Die Wirkung bleibt zu hinterfragen, da sie sich bei einer weiteren Studie mit einer höheren Anzahl von Versuchspersonen nicht replizieren ließ (Keune, Bostanov, Hautzinger, & Kotchoubey, 2011). Allerdings könnte die Stichprobenwahl eine Rolle spielen, da alle Patienten bei Barnhofer et al. (2007) in ihrer Vorgeschichte Suizidalität aufwiesen, bei Keune et al. (2011) zeigten die Patienten dieses Merkmal nicht. Auch wurde in beiden Studien nicht kontrolliert, inwieweit die Meditationen zwischen den therapeutischen Sitzungen von den Patienten tatsächlich durchgeführt wurden. Ein divergierendes Ausmaß an Meditation könnte zu den verschiedenen Ergebnissen beitragen haben.

Interessant wäre, ob genannte Behandlungsstrategien einen zusätzlichen Einfluss auf die Aktivität des Gefahrerkennungssystems und/oder des Vermeidungssystems haben, da bestehende Behandlungsmethoden diese vermutlich schon indirekt verändern. So könnte eine Therapie mit Expositionen zu einer Desensibilisierung des Gefahrerkennungssystems und einer geringeren Aktivität des Vermeidungssystems führen. Beispielsweise wurde bei anderen Patientengruppen eine Veränderung der Aktivität des Vermeidungssystems durch eine

psychotherapeutische Behandlung nachgewiesen. So wurde in Studien bei Patienten mit sozialer Phobie (Moscovitch et al., 2011) und bei Patienten mit einer Posttraumatischen Belastungsstörung (Rabe, Zoellner, Beauducel, Maercker & Karl, 2008) nach einer kognitiven Verhaltenstherapie eine verstärkte Aktivierung des Annäherungssystems im Verhältnis zum Vermeidungssystem gemessen. Es wurden auch Effekte von Behandlungen auf andere Temperamentmerkmale von Patienten nachgewiesen. So führte beispielsweise eine kognitive Verhaltenstherapie bei Patienten mit Essstörungen (Dalle Grave et al., 2007) und eine psychopharmakologische Behandlung bei Patienten mit Zwangsstörungen (Lyoo, Yoon, Kang & Kwon, 2003) zu einer Reduktion der Persönlichkeitseigenschaft der Schadensvermeidung. Um dies bezüglich die Aktivität des Gefahrerkennungssystems und/oder des Vermeidungssystems bei Patienten mit Zwangsstörungen zu überprüfen, müsste eine Studie die Aktivität vor der Behandlung mit der Aktivität danach vergleichen. Anschließend könnten die Effekte einer kognitiven Verhaltenstherapie mit einer Behandlung, welche durch die oben genannten zusätzlichen Behandlungsstrategien ergänzt wurde, verglichen werden.

Schließlich könnten die Befunde der ersten durchgeführten Studie innerhalb einer Psychotherapie im Rahmen der zu Beginn stattfindenden Psychoedukation eingesetzt werden. Beispielsweise könnte ein hyperaktives Gefahrerkennungssystem der Patienten als beteiligter Grund für die Erkrankung benannt werden. Diese wertschätzende Konnotation der Störung könnte dazu führen, dass sich Patienten eher verstanden fühlen und sich damit die Therapeut-Patienten-Beziehung verbessert. Dies könnte wiederum in einer niedrigeren Abbruchrate resultieren.

Limitationen der vorliegenden durchgeführten Studien ergeben sich aus der Stichprobenzusammensetzung der Patientengruppen. Neben Patienten mit komorbiden depressiven Störungen waren auch solche eingeschlossen, die sich in psychopharmakologischer Behandlung befanden. Ein hieraus resultierender Einfluss auf die Ergebnisse lässt sich nicht ausschließen. Demzufolge ist es erstrebenswert, die Ergebnisse bei Patienten mit Zwangsstörungen zu replizieren, die keine Komorbiditäten zeigen und sich nicht in einer aktuellen (vor allem psychopharmakologischen) Behandlung befinden. Allerdings stellt sich bei solch strengen Ausschlusskriterien die Frage, inwiefern sich die Befunde auf die allgemeine Patientenpopulation übertragen ließe, welche durch Komorbiditätsraten von bis zu 90% gekennzeichnet ist (Ruscio et al., 2010).

Zusammenfassend lässt sich formulieren, dass Veränderungen in der emotionalen Reizverarbeitung bei Patienten mit Zwangsstörungen festgestellt wurden. Diese Überaktivierungen von evolutionär sinnvollen Systemen könnten sowohl bei der Entwicklung

als auch bei der Aufrechterhaltung der Störung eine wichtige Rolle spielen und ließen sich in das kognitive Modell der Zwangsstörung von Salkovskis (1999) einordnen. Gerade im Hinblick auf die psychotherapeutische Behandlung ergeben sich hierdurch wichtige Fragestellungen, welche in weiterführenden Studien untersucht werden sollten.

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# 5 Wissenschaftliche Artikel

## 5.1 Publikation

**Ischebeck, M.**, Endrass, T., Simon ,D. & Kathmann, N. (2011). Auditory novelty processing is enhanced in obsessive-compulsive disorder. *Depress Anxiety,* 28(10):915-23. doi: 10.1002/da.20886.

## 5.2 Manuskript

**Ischebeck, M.**, Endrass, T., Spielberg ,R. & Kathmann, N. Novelty processing in obsessive-compulsive disorder. An event-related potential study.

## 5.3 Eingereichtes Manuskript

**Ischebeck, M.**, Endrass, T., Simon ,D. & Kathmann, N. Frontal EEG asymmetry in obsessive-compulsive disorder. *Psychophysiology*, manuscript in revision.

*DEPRESSION AND ANXIETY 28 : 915–923 (2011)*

*Research Article*

# AUDITORY NOVELTY PROCESSING IS ENHANCED IN OBSESSIVE–COMPULSIVE DISORDER

Moritz Ischebeck, Dipl.-Psych.,* Tanja Endrass, Ph.D., Daniela Simon, Ph.D., and Norbert Kathmann, Ph.D.

**Background:** *Cognitive models propose that anxiety disorders are associated with an attentional bias toward potentially threatening stimuli. In this study, it was analyzed whether patients with obsessive–compulsive disorder (OCD) show enhanced responses of their event-related brain potentials to novel stimuli, either in a context of potential threat or in a neutral context.* **Methods:** *In this study, 20 OCD patients and 20 matched healthy control subjects performed a visual recognition task during which irrelevant repeated standard sounds and unitary novel sounds were interspersed.* **Results:** *As expected, OCD patients showed an increase in the novelty-P3 amplitude elicited by unitary novel sounds. However, no effect of emotional context conditions was observed.* **Conclusion:** *It is suggested that the novelty P3 amplitude increase in OCD patients represents a physiological indicator of an enhanced cortical orienting response implicating stronger involuntary shifts of attention. This characteristic is driven by novelty per se and not moderated by potential threat of upcoming events. Depression and Anxiety 28:915–923, 2011.* 

**Key words:** *OCD; anxiety disorder; P3 amplitude; electroencephalography; orienting response*

## INTRODUCTION

Obsessive–compulsive disorder (OCD) is an anxiety disorder characterized by intrusive thoughts, referred to as obsessions and ritualized and repeated behavior or mental acts, referred as compulsions.[1] According to cognitive models, patients suffering from anxiety disorders show an attentional bias toward threatening stimuli.[2–6] Consequently, it is assumed that a threat detection system, which is hypersensitive for potentially relevant or threatening stimuli, operates stimulus-driven in an automatic mode at an early processing stage.

Experimental research has shown that OCD patients perform abnormally in attentional tasks.[7] In a dichotic listening paradigm, more fear-related than neutral words were detected by OCD patients in the unattended ear.[8] In the emotional Stroop task, OCD patients evidenced longer response latencies to fear-related words than to neutral words.[9–12] Furthermore, in a dot probe paradigm OCD patients detected dots faster at the location where a threat word had appeared 500 ms before.[13] These results were interpreted as an automatic attentional bias toward potentially threatening stimuli. However, the use of these paradigms as measures of automatic attentional processing has also been criticized. It has been argued that they tap not only early attentional processes in terms of an automatic shift of attention toward threat-related stimuli but also late processes of attention including attentional control mechanisms[14] or disengagement effects.[15] Behavioral studies so far seem to measure the interaction of two attentional systems, a stimulus-driven (bottom-up) system and a goal-directed (top-down) system.[16] Thus, clear evidence for a hypersensitivity of the stimulus-driven attentional system[5] in OCD has not been provided yet.

The automatic threat detection system[17] should be assessable in the orienting response of attention toward

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unexpected stimuli because such a response is a necessary prerequisite for rapid assessment of potential harm.[18] The orienting response, which includes involuntary shifts of attention toward novel and potentially relevant stimuli,[19,20] is characterized by skin conductance increase, heart rate deceleration, and a cortical orienting response, measurable in the endogenous event-related brain potential (ERP).[21] A specific cortical correlate of the orienting response is the novelty P3.[22,23] This component might be especially interesting in OCD research because it has generators in the anterior cingulate cortex (ACC) and the orbitofrontal cortex.[24,25] Remarkably, these areas play a major role in current pathophysiological models of OCD proposing hyperactivity within frontostriatal brain circuits as a central feature of the disorder.[26–28] These brain regions are also implicated in a stimulus-driven frontal right-hemispheric attentional network system, with dopamine as the most significant neurotransmitter involved.[29] For instance, healthy subjects having a genetic variant associated with higher striatal dopamine show larger novelty P3 amplitudes and get more distracted by novel sounds.[30] Dopamine also appears to be implicated in the pathophysiology of OCD.[31,32]

Enhanced novelty P3 amplitudes have been found in patient groups with mixed anxiety disorders,[33] post traumatic stress disorder[34] and in healthy individuals during states of increased anxiety.[35] In addition, heightened P3 amplitudes following target sounds have been found in OCD patients.[36,37]

In this study, a visual recognition task was used, with irrelevant auditory novel stimuli interspersed to elicit the novelty P3. The aim was to test whether the cortical response to stimulus novelty is enhanced in OCD. A second aim was to clarify the effect of context in which novel events occur. Earlier studies found enhanced novelty P3 amplitudes in a negative emotional context.[18,38] Therefore, it appeared possible that enhanced novelty responses in OCD patients are elicited only in a negative emotional context. To investigate this, two conditions were created: a neutral condition in which the participants saw neutral pictures only, and a negative condition where both neutral and aversive pictures were randomly intermixed to induce a potentially threatening, negative emotional context. Because the participants' task was to attend and to respond to the repetition of visual stimuli, this paradigm allowed measuring the auditory novelty P3 outside the focus of attention therefore reflecting the automatic orienting of attention to novel events. To our knowledge, this is the first study investigating the novelty P3 in OCD. We hypothesize that a hypersensitive threat detection system in OCD patients evokes increased cortical orienting responses reflected in enhanced novelty P3 amplitudes compared to healthy control participants. Since the novelty P3 is enhanced by negative emotional context, we predict that the

**TABLE 1. Age at illness onset, comorbidity and medication of OCD patients**

| Patient no. | Age at illness onset (years) | Comorbid disorders | Medication |
|---|---|---|---|
| 1 | 33 | None | None |
| 2 | 22 | None | None |
| 3 | 20 | None | None |
| 4 | 8 | Major depressive affective disorder recurrent episode in full remission (296.36) | None |
| 5 | 40 | None | None |
| 6 | 20 | None | None |
| 7 | 26 | None | Citalopram |
| 8 | 7 | None | Escitalopram |
| 9 | 8 | Major depressive affective disorder recurrent episode in full remission (296.36) | Paroxetine |
| 10 | 18 | Major depressive affective disorder single episode mild degree (296.21) | Clomipramine |
| 11 | 4 | Anorexia nervosa (307.1), Major depressive affective disorder recurrent episode in partial or unspecified remission (296.35) | Citalopram |
| 12 | 31 | None | Fluoxetine |
| 13 | 9 | None | None |
| 14 | 6 | None | Escitalopram |
| 15 | 7 | Major depressive affective disorder single episode mild degree (296.21) | None |
| 16 | 4 | Social phobia (300.23) | None |
| 17 | 18 | Social phobia (300.23) | Clomipramine |
| 18 | 18 | None | Clomipramine |
| 19 | 10 | None | Clomipramine |
| 20 | 10 | None | None |

OCD, obsessive–compulsive disorder.

group difference in the novelty P3 should be enlarged in the negative context condition.

# MATERIALS AND METHODS

## SUBJECTS

Twenty OCD patients (7 males, 13 females) participated in this study. They were recruited from the outpatient clinic of the Department of Psychology at Humboldt-Universität zu Berlin. Patients were diagnosed to have OCD according to the DSM-IV criteria [American Psychiatric Association, 1994]. To validate diagnoses, patients were interviewed using the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders.[39] Exclusion criterion was the presence of neurological illness. OCD was the primary diagnosis in all patients, while seven patients had comorbid diagnoses (Table 1). On average, patients had moderate OCD symptoms and mild depressive symptoms (Table 2). Half of the patients were medicated (Table 1). Patients were matched with 20 control subjects with respect to gender, age, and verbal intelligence (Table 2). Verbal intelligence was assessed by a German Vocabulary Test (Wortschatztest[40]). All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory.[41] Subjects provided written informed consent. The study protocol was approved by the ethical review board of the Medical Department Charité, Berlin.

## TASK

During a visual recognition task, subjects were presented with task irrelevant standard and novel sounds. The 600 sound presentations included 120 novels ($P = .2$) and 480 standard stimuli ($P = .8$). The standards were 600 Hz tones, and the novels were nonrecurring complex sounds (as described in Reference[42]). All auditory stimuli had a duration of 200 ms and were delivered via speakers at 50 dB above individual hearing thresholds, as measured by audiometry.

To set a specific emotional context, the visual recognition task was performed under two different conditions. In the neutral condition, only pictures with neutral affective valence were presented. In the negative condition, half of the pictures had negative valence, and half of the pictures were neutral. Each picture was presented five times. On each picture presentation subjects were asked to decide whether the picture was new or they saw it before. Pictures were taken from the International Affective Picture System [43]. Thirty negative pictures (NegP), and 90 neutral pictures (NeuP) were selected according to published ratings.[43] We did not include pictures which were obviously symptom-related to avoid individual- and symptom-specific effects (for example picture 9,300 might trigger contamination/cleaning OCD symptoms). Negative and neutral picture sets differed significantly with respect to valence (mean: NegP = 2.41, NeuP = 5.08; $t(118) = 28.55$, $P < .001$) and arousal (mean: NegP = 6.23, NeuP = 2.01 $t(118) = -27.85$, $P < .001$).

**TABLE 2. Sociodemographic and clinical characteristics of OCD patients and healthy control subjects**

| | Healthy controls | OCD patients |
|---|---|---|
| *N* | 20 | 20 |
| Gender (Males/females) | 7/13 | 7/13 |
| Age (years) | 32.7 (9.3) | 32.8 (9.9) |
| Years of education | 12.4 (1.2) | 12.4 (1.2) |
| Verbal IQ | 109.8 (8.1) | 107.5 (7.5) |
| YBOCS | – | 19.6 (6.5) |
| OCI-R | 6.9 (6.0) | 29.0 (15.9) |
| MADRS | – | 11.4 (9.7) |
| BDI | 2.8 (3.3) | 13.4 (9.3) |
| STAI–T | 33.5 (9.3) | 49.5 (11.6) |
| STAI–S prior to experiment | 32.9 (7.1) | 41.0 (10.1) |
| STAI-S after the low state anxiety condition | 32.9 (7.3) | 40.8 (8.5) |
| SIAI-S after the high state anxiety condition | 32.6 (7.4) | 42.5 (9.1) |

Numbers, means and standard deviations (in parentheses) are reported.

Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory-Revised; MADRS, Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory; STAI-T, Trait version of State-Trait Anxiety Inventory; STAI-S, State version of State-Trait Anxiety Inventory.

## PROCEDURES

The instruction screen taught the subjects to press a key with the index finger of one hand whenever they saw a picture for the first time and another key with the index finger of the other hand when they had seen the picture before. After 10 practice trials, using different stimuli, two blocks with the two conditions followed, each consisting of 300 trials with a short break in-between. The trials had the following sequence: subjects focused on a fixation cross for 2,400 ms. During this time, a sound was presented either 1,200, 1,300, 1,400, or 1,500 ms after fixation cross onset. These time windows were chosen to reduce expectancy effects. Immediately following the fixation cross, a picture was presented for 1.0 s. This frame was replaced by a new one displaying the words "old" and "new" appearing on the left and right side of the screen for 900 ms. Responses had to be executed within a 1,900-ms interval after decision cue onset, otherwise subjects were reminded to respond faster until they pressed one key. Sounds and pictures were pseudo-randomized, and the sequence of condition blocks was counterbalanced across subjects. Prior to the first block, between blocks, and after the second block subjects filled in the state version of the State-Trait Anxiety Inventory (STAI[44]). After having completed the task, subjects rated the pictures regarding arousal and unpleasantness. Patients were additionally asked to rate the urge to execute compulsions provoked by each picture.

We modified the structure of the task used in earlier studies.[18,38] By intermixing negative with neutral pictures in the negative condition, we aimed to look at the orienting response during anticipation of a possible and not a certain threat. This was inspired by a study by Grillon et al.[35] using a similar structure, in which the participants anticipated an electric shock in the threat condition; and, second, by the fact that anticipation of possible threats is a prominent clinical feature of OCD. A larger interstimulus interval was chosen in order to avoid intermixing of sound and picture processing and further to keep the sounds as task irrelevant as possible.

## EEG RECORDING

The electroencephalogram and the electrooculogram were recorded from 64 electrode sites using *BrainAmp* EEG amplifiers and *BrainVision* Recorder software (Brainproducts, Munich, Germany). An *EasyCap* electrode cap system (Falk Minow Services, Munich, Germany) was employed, with electrodes placed concentrically. All electrode impedances were kept below 5 kΩ. The recordings were referenced to activity at Cz. Signals were digitized with a sampling rate of 500 Hz and amplified with a filter band pass of 0.01–100 Hz.

## DATA ANALYSIS

**Behavioral data.** Reaction times and hit rates were compared between groups (patients versus controls) by using analysis of

variance (ANOVA). Within-subjects factors were emotion of the pictures (neutral in the neutral context versus negative in the intermixed context) and the type of the sound preceding the picture presentation (standard versus novel).

**ERP methods.** EEG data were digitally filtered with a low-pass filter at 40 Hz. The EEG was then re-referenced off-line to average reference and corrected for eye movement artifacts using the multiple source eye correction method [45] implemented in BESA (Brain Electrical Source Analysis, v 5.1; MEGIS Software GmbH, Gräfeling, Germany). Stimulus-locked epochs between 100 ms pre- and 900 ms post-stimulus were extracted, and artifact-contaminated epochs were rejected. The 100-ms interval preceding stimulus onset served as baseline. Following SanMiguel et al.[46] the novelty P3 was measured in the difference waves obtained by subtracting the ERPs elicited by standard tones from those elicited by novel sounds. Amplitude was measured as mean voltage in a 50-ms time window (290–340 ms) around the peak of the grand-average waveform at electrode site FCz where the largest amplitude was found. Statistical analysis of the novelty P3 amplitude was conducted using ANOVA with the between-subjects factor group (patients versus controls), and the within-subjects factors context (neutral versus negative), hemisphere (left versus right), and anterior–posterior scalp axis (posterior versus anterior). Electrodes FC3, F1, C3, FC1 (left anterior), F2, FC4, FC2, C4 (right anterior), CP3, CP1, PO3, P1 (left posterior), and CP2, CP4, P2, PO4 (right posterior) were included in the analyses. To test possible medication effects, this ANOVA was redone within the patient group using the additional between-subjects factor medication (medicated versus non-medicated). We further tested the source of significant differences (standards or novels) by performing an ANOVA on original ERP components using the additional factor sound type (standard versus novel). In post hoc analyses, we added FCz, because at this site the largest amplitudes were measured. Latency of the novelty P3 was determined at FCz.

# RESULTS

## BEHAVIORAL PERFORMANCE

Overall performance was high with an average of 91.5% correct responses with no significant differences between groups. There was also no difference between groups regarding response times. Further, behavioral data were analyzed for effects of sound novelty and context. There was a main effect of sound novelty on reaction times reflected by slower responses to pictures which were preceded by novel sounds ($F(1, 38) = 20.54$, $P<.001$). There was a main effect of emotion characterized by slower responses and higher hit rates to negative than to neutral pictures ($F(1, 38) = 5.75$, $P=.021$; $F(1, 38) = 55.25$, $P<.001$, respectively). No interactions were found for these factors with diagnostic group.

## PICTURE RATINGS

Comparing the picture sets across groups, we replicated the findings of Lang et al.[43] Pictures from the negative set had a more negative valence than pictures from the neutral set (mean: NegP = 2.98, NeuP = 6.43; $t(39) = 18.41$, $P<.001$). Arousal was also rated higher in the negative set compared to the neutral set (mean: NegP = 6.77, NeuP = 3.51; $t(39) = 15.79$, $P<.001$). There were no significant group differences in these ratings. Patients rated OCD symptoms provoked by the pictures overall as low, with significant higher ratings for negative pictures (mean: NegP = 2.72, NeuP = 1.68; $t(39) = 3.29$, $P<.01$) (Table 3).

**TABLE 3. Picture ratings for neutral and negative pictures (group means and standard deviations)**

| | Healthy controls | OCD patients |
|---|---|---|
| *Neutral pictures* | | |
| Valence | 6.4 (0.7) | 6.4 (1.0) |
| Arousal | 3.5 (0.9) | 3.5 (1.0) |
| OCD symptoms | – | 1.7 (0.8) |
| *Negative pictures* | | |
| Valence | 2.9 (0.9) | 3.0 (0.7) |
| Arousal | 6.7 (0.9) | 6.8 (0.8) |
| OCD symptoms | – | 2.7 (2.0) |

(Valence rating: 1 = very unpleasant; 9 = pleasant arousal rating: 1 = calming; 9 = very arousing; provocation rating: 1 = not at all; 9 = very strong).

## ANXIETY SELF-REPORTS

Patients had significantly higher trait anxiety, as measured with the trait version of the STAI compared to the healthy control subjects ($t(39) = 4.85$, $P<.01$).

Analyzing the state version of the STAI using ANOVA with the between-subjects factor context (after neutral block versus after negative block), a significant difference between OCD patients and healthy control subjects was found ($F(1, 38) = 13.25$, $P<.001$). Neither a significant main effect of context nor a significant interaction group × context was found. Patients reported significantly more state anxiety already prior to the experiment ($t(39) = 2.92$, $P<.01$).

## EVENT-RELATED POTENTIALS

[1]P3 amplitudes elicited by novel stimuli were compared between groups in two conditions. The

[1]The N1 and MMN were analyzed to examine group differences in earlier attentional processes. We performed an analysis of variance (ANOVA) with the between-subjects factor group (patients versus controls), and the within-subjects factors context (neutral versus negative) and sound novelty (standard versus novel sound) for the N1. The mean amplitudes of N1 were measured in the time window of 100–150 ms at fronto-central electrode locations (F1, Fz F2, FC1, FCz, FC2, CP1, Cz, and CP2). We found a trend toward a significant main effect of the factor group ($F = 3.51$; $P = .069$), due to higher N1 amplitudes in control participants, suggesting better sensory processing in control subjects. There was no significant interaction of group and context, group and sound nor group, context and sound (all $P>.70$). In an ANOVA for the MMN, we included the between-subjects factor group (patients versus controls), and the within-subjects factor context (neutral versus negative). The MMN mean amplitudes were obtained from the difference waves novel minus standard sound in the time window of 170–270 ms at the following

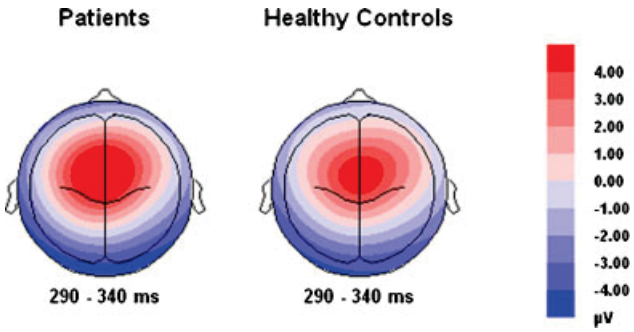


**Figure 1. Topographical ERP scalp distribution maps (equidistant projection 90°) of the novelty P3 in patients and healthy control subjects (290–340 ms). ERP, event-related brain potential.**

factors hemisphere[2] and anterior–posterior scalp axis[2] were added to look for topographic differences. The hypothesized difference between OCD patients and healthy control subjects was confirmed, as the main effect of groups was significant, $F(1, 38) = 5.48$, $P = .025$. Furthermore, the significant interaction of laterality × group, $F(1, 38) = 4.89$, $P = .033$, revealed a topography-specific alteration of the novelty P3 amplitude (Fig. 1). This was confirmed in post hoc *t*-tests: in the negative condition, larger novelty P3 amplitudes were observed in patients at a central site (FCz, $P < .05$), left anterior sites (FC3, $P < .01$; F1, $P < .05$; C3, $P < .01$; FC1, $P < .05$), and left posterior sites (CP3, $P < .01$; CP1, $P < .05$; P1, $P < .05$) (Fig. 2). In the neutral condition, post hoc *t*-tests revealed larger novelty P3 amplitudes in patients at the central site (FCz, $P < .05$), and at left anterior sites (FC3, $P < .05$; F1, $P < .05$; FC1, $P < .05$). These results indicate that patients differed from healthy controls primarily at left and central areas (Fig. 3).

A significant main effect for the factor posterior–anterior scalp axis, $F(1, 38) = 157.09$, $P < .001$, and a significant interaction of laterality × posterior–anterior axis, $F(1, 38) = 10.61$, $P = .002$, revealed the expected anterior right-sided topography of the novelty P3 (Fig. 1). Moreover, there was a significant interaction of laterality × condition, $F(1, 38) = 7.29$, $P = .010$. Post hoc comparisons within each hemisphere did not reveal a significant main effect of condition in either the left, $F(1, 38) = 1.76$, $P = .193$, or the right hemisphere, $F(1, 38) = 0.38$, $P = .540$, suggesting that differences resulted from small changes of activity in both the left and the right hemisphere, rather than being driven by one hemisphere alone. Further post hoc comparisons

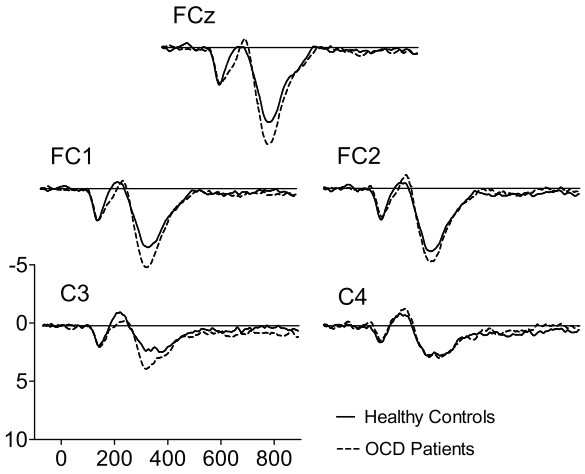


**Figure 2. Grand-average novel-standard difference waves of OCD patients and healthy controls in the negative context condition. Electrodes used in the data analysis are depicted.**

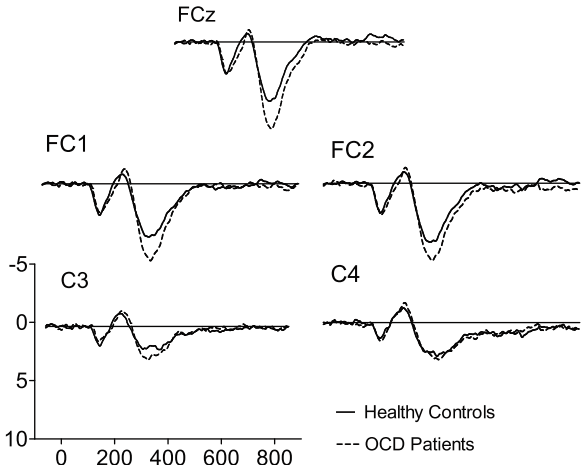


**Figure 3. Grand-average novel-standard difference waves of OCD patients and healthy controls in the neutral context condition. Electrodes used in the data analysis are depicted. OCD, obsessive–compulsive disorder.**

within each condition did not reveal a significant main effect of hemisphere in either the neutral, $F(1, 38) = 3.50$, $P = .07$, or the negative condition, $F(1, 38) = 0.74$, $P = .394$.

The analysis of the original ERP data revealed a significant interaction of group and sound novelty ($F(1, 38) = 5.72$; $P = .022$). Followup test showed that this interaction was due to differences between groups in the P3 waves following novel sounds ($F(1, 38) = 4.86$; $P = .034$) and not following standard sounds ($F(1, 38) = .68$; $P = .416$). We further observed significant interactions between sound novelty, hemisphere, and group ($F(1, 38) = 4.62$; $P = .038$), and between sound novelty, conditions, and hemisphere ($F(1, 38) = 8.14$; $P = .007$). We did neither observe an interaction

(*footnote continued*)
electrodes: FC1, FCz, FC2, Cz, CP1, CPz, and CP2. There was neither a significant main effect of group nor a significant interaction of group and context (all $P > .70$). Taken together, these results support that our effects in the novelty P3 were not due to enhanced sensory processing (N1) or automatic change detection (MMN) in OCD patients.

between group and condition nor an interaction between group, sound, and condition.

No group differences were found for novelty P3 latency.

### ANALYSES OF MODERATOR VARIABLES

There were no correlations between the novelty P3 amplitudes and scores of MADRS, BDI, YBOCS, OCI, or STAI. There was no significant main effect of medication on novelty P3 amplitudes, $F(1, 18) = .42$, $P = .527$ (medicated patients $M = 3.39$, $SD = .37$, unmedicated patients $M = 3.05$, $SD = .37$, control participants $M = 2.37$, $SD = .23$), no interaction of medication × condition, $F(1, 18) = .44$, $P = .518$ or medication × hemisphere, $F(1, 18) = .98$, $P = .336$. Moreover, there was no significant effect of gender or age at onset of disease.

## DISCUSSION

This study investigated novelty processing in OCD patients in neutral and negative emotional contexts. Our results support the hypothesized enhancement of the novelty P3 in OCD patients compared to healthy control subjects. Scalp distribution of the novelty P3 was less lateralized in patients than in controls. The expected influence of negative context leading to a larger novelty P3 amplitude was not found either in patients or in healthy control subjects, and did not moderate group differences (Fig. 4).

The increased novelty P3 in OCD patients might reflect an enhanced orienting response toward unexpected stimuli. It thereby supports the idea of a hypersensitivity of the stimulus-driven attentional system which could go beyond emotional relevance toward salient stimuli in general. This interpretation is

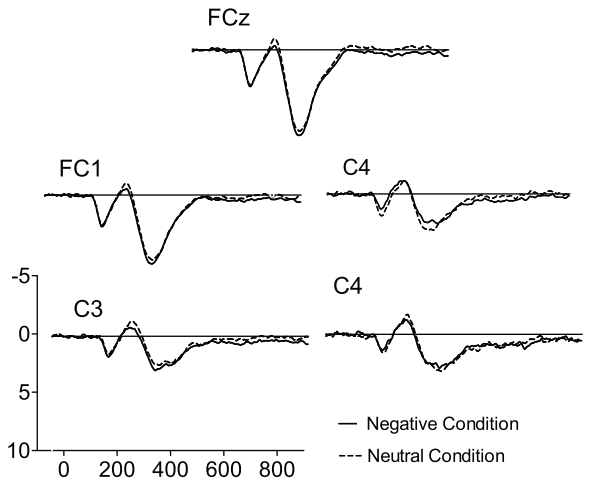


**Figure 4. Grand-average novel-standard difference waves in the neutral and negative context condition (across group) Electrodes used in the data analysis are depicted. OCD, obsessive–compulsive disorder.**

in line with other findings in OCD. Towey et al.[47] found enhanced P3 amplitudes for unattended nontargets and an enhancement of the processing negativity, suggesting dysfunctional hyperattention. Clayton et al.[48] found lower scores for the subtest selective attention of the test of everyday attention [49] in patients with OCD. This was interpreted as expression of OCD patients' reduced ability to selectively ignore stimuli. In an eye-tracking experiment, Armstrong et al.[50] found that students with high contamination fears show enhanced orienting responses toward fearful faces.

The results of this study are in line with those found in other anxiety disorders,[33,34,51] whereas reduced novelty P3 amplitudes have been reported for depressive disorders.[52,53]

Impaired selective attention might play an important role for the onset and maintenance of anxiety disorders.[54] Reeb-Sutherland et al.[55] found that individuals with high levels of behavioral inhibition and increased novelty P3 amplitudes were more likely to have a history of anxiety disorders. Therefore, it is a promising hypothesis that hypersensitivity of the stimulus-driven attentional system is involved in the development and course of anxiety disorders as a crucial factor.

Mobini and Grant[56] discussed important implications of research on the negative attentional bias for clinical practice. This reasoning could be transferred to findings of attentional bias toward salient stimuli in general. The conclusion would be that it appears important to modify existing cognitive behavioral psychotherapy (CBT) techniques. The hypersensitivity of the stimulus-driven attentional system might be a reasonable focus in therapy. However, it is probably challenging to modify attentional bias, as such processes are largely involuntary.[56] Hypersensitivity to novel events can be addressed directly through extinction learning and habituation, but other techniques might also be useful. For example, attention plays an important role in mindfulness-based treatments.[57] These treatments incorporate meditation practice which is known to affect attention.[58] Interestingly, Vipassana meditators showed reduced attentional engagement elicited by unexpected and distracting stimuli.[59] Therefore, meditation practice might be a promising additional method to influence dysfunctional hyperattention. Preliminary evidence of effectiveness of these interventions in OCD has already been reported,[60,61] though there is still a need for further research in this field.

In this study, it remained unclear how the stimulus-driven attentional system is affected by a negative emotional context. Although the negative emotional context led to topographic changes of the novelty P3, driven by both hemispheres, and negative pictures did evoke more attention processing, as measured by longer reaction times and hit rate, our manipulation of context was not capable to enhance cortical novelty

responses. This issue needs to be further investigated. According to Bradley,[21] the orienting response is a biologically adaptive physiological response that is part of our defensive behavior and provides us with information about possible threats. Further, there are few findings of increased novelty processing in a negative context,[18,38] and under the anticipation of shock.[35] These results point toward higher recruitment of attentional resources in negative emotional context when unexpected, and therefore potentially threatening stimuli are presented. One reason for the lack of an effect in this study might be the timing of stimulus presentation. Although in earlier studies the sounds were processed during picture presentation, in this study, pictures and sounds were presented subsequently. The timing of stimulus presentation in this study might also explain that we failed to find group differences in reaction times to pictures that were preceded by novel sounds (as compared to standard sounds). The absence of the expected interaction of context and group might also be due to the mixing of negative with neutral pictures in the negative condition instead of presenting only negative pictures, possibly leading to a smaller influence of the negative emotional context. Another factor might be the emotional intensity of the negative images. The images used in earlier studies[18,38] included scenes of extreme violence and disgust. In the present experiment, pictures with extreme negative valence were not used because we did not want to provoke OCD symptoms. Finally, it is possible that the task was more difficult than that in earlier studies,[18,38] and thereby engaged additional cognitive resources. Further research should clarify whether the degree of affective valence determines novelty processing.

In accordance with previous reports, a right hemispheric lateralization of the novelty P3 was found in healthy subjects.[16,62,63] In contrast, patients showed less lateralization of the novelty P3, and group differences therefore emerged over the left hemisphere (Fig. 1). Topographical alterations of ERP waves in OCD patients have already been reported in other studies. In a classic oddball paradigm, Morault et al.[64] found a left hemispheric lateralization of the target P3 in OCD patients compared to a right hemispheric lateralization in control subjects. Moreover, Tot et al.[65] found frontal left hemispheric differences in OCD patients compared to control subjects in $\alpha$, $\beta$, $\delta$ and $\theta$ bands using quantitative electroencephalographic measurements. In a magnetic resonance imaging study, Shim et al.[66] found that OCD patients showed differences to control subjects in the left ACC which is interesting in the light of the assumed role of the ACC in the generation of the novelty P3 amplitude. Generally, evidence is accumulating that left hemisphere abnormalities can be observed in OCD patients. It needs additional and more sophisticated methods to reveal the mechanisms generating these alterations.

Some limitations of this study should be noted. First, it includes patients who were taking psychotropic medications. To control for medication effects, patients with and without medication were compared, and no significant differences were found. Second, several patients had comorbid depressive disorder. Because reduced novelty P3 amplitudes have been shown in patients with depression,[52,53] it might be that novelty P3 differences would appear even larger when patients have no comorbid depression. Nevertheless, to control for confounds it would be advantageous to analyze an OCD sample without medication and comorbidity. Third, the structure of the task used in this study differed from earlier studies making it difficult to directly compare results between these studies.

In conclusion, we found increased cortical orienting responses in OCD patients toward novel stimuli, as measured with the novelty P3 amplitude of the EEG. The group differences were independent of the emotional context. Increased P3 amplitudes were observed over central and left anterior scalp regions. Findings are in accordance with the assumption of a hypersensitive stimulus-driven attention system which appears to characterize in anxiety disorders in general, distinguishing them from mood disorders. As selective attention, including increased attention toward unexpected and potentially threatening stimuli, might play an important role for the development and maintenance of anxiety disorders, it might be a reasonable focus of psychotherapy.

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# Novelty processing in obsessive-compulsive disorder:

# An event-related potential study.

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## Abstract

Cognitive models propose that anxiety disorders are associated with a threat detection system that is hypersensitive for potentially relevant or threatening stimuli (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998). This should be assessable in the orienting of attention towards novel, unexpected stimuli, because this is a necessary perquisite for rapid awareness to potential harm. The orienting response includes involuntary shifts of attention towards novel and potentially relevant stimuli (Parmentier, 2008; Sokolov, 1990) and can be measured with the novelty P3, an event related potential. Recently, a heightened novelty P3 was found in patients with obsessive-compulsive disorder (OCD) in a passive auditory attentional mode task (Ischebeck, Endrass, Simon, & Kathmann, 2011). The aim of the current study was to investigate whether enhanced novelty processing is present during an active attentional condition. Hence, we conducted a three-stimulus novelty oddball paradigm to compare the novelty P3 in OCD patients to the novelty P3 in healthy control subjects. No significant differences were found. The results were compared with earlier findings and suggest that only passive attentional conditions induce enhanced orienting to novel stimuli.

## Introduction

According to cognitive models, anxiety disorders are associated with an attentional bias towards threatening stimuli, which is partially due to a threat detection system that is hypersensitive for potentially relevant or threatening stimuli (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998). This system seems to function automatically at an early processing stage (Mathews & Mackintosh, 1998) and performs a rudimentary analysis to provide a coarse and rapid assessment (Morris, Ohman, & Dolan, 1999). Accordingly, the threat detection system might rely on the input of a stimulus-driven attentional system, which should be assessable in the orienting of attention towards unexpected stimuli, because this is a necessary perquisite for rapid awareness to potential harm (Garcia-Garcia, Dominguez-Borras, SanMiguel, & Escera, 2008). The orienting response includes involuntary shifts of attention towards novel and potentially relevant stimuli (Parmentier, 2008; Sokolov, 1990). A cortical correlate of the orienting response in the event-related potential (ERP) is the novelty P3 (Barry, Macdonald, & Rushby, 2010). Abnormalities of the novelty P3 were found in anxiety disorders (ERP; Bruder et al. (2002)). More specifically, increased novelty P3 was found in patients post traumatic stress disorder (Kimble, Kaloupek, Kaufman, & Deldin, 2000). Moreover, enhanced novelty P3 was also observed in healthy individuals showing increased state anxiety (Grillon & Ameli, 1994).

Recently we observed heightened novelty P3 in patients with an obsessive-compulsive disorder (OCD; Ischebeck et al. (2011)) following novel auditory stimuli, which were not task-relevant and to which patients where passively listening to. The interpretation of the heightened novelty P3 as the result of a hypersensitive threat detection system was insensitive to the influence of emotional context. However in

another study the novelty P3 modulation in healthy individuals with state anxiety varied with attention (Grillon & Ameli, 1994). The heightened novelty P3 under increased state anxiety was only observed while the subjects were passively listening to the auditory stimuli (passive attentional mode). It was not observed, when the subjects had to press a button in response to target stimuli (active attentional mode). Therefore it seems to make a difference, if the novel stimuli are listened to in active compared to passive attentional mode.

The aim of the current study was to investigate whether novelty P3 amplitudes in OCD depended on attentional processes. In particular, we examined whether the previously fond enhanced novelty P3 in a passive attentional condition (Ischebeck et al., 2011) would be replicated in an active attentional condition. Therefore, we employed a three-stimulus novelty oddball paradigm in the present study, in which the subjects had to press a button following target stimuli.

To our knowledge, no study so far analyzed the novelty P3 in an active attentional condition in subjects suffering from OCD. Following the findings of a heightened novelty P3 in anxiety patients in active attentional mode (Kimble et al., 2000), we hypothesize, that the heightened novelty P3 in OCD patients found in passive attentional mode will be replicated in active attentional mode.

## Materials and Methods

### Subjects

Twenty patients with OCD (10 males, 10 females) participated in this study. They were referred from the outpatient clinic of the Department of Clinical Psychology at Humboldt-Universität zu Berlin. Patients were diagnosed with OCD according to the DSM-IV criteria [American Psychiatric Association, 1994]. They were

interviewed using the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Gibbon, Hilsenroth, & Segal, 2004). Patients reported to have no neurological disorders or other potentially interfering diseases. OCD was the primary diagnosis in all patients, while ten patients had comorbid diagnoses, most of them major depressive disorder (table 1). On average the patients had moderate OCD symptoms and only mild depressive symptoms (table 2). Thirteen of the patients were medicated (table 1). Patients were matched with 20 control subjects with respect to gender, age, and verbal intelligence (table 2). Verbal intelligence was assessed by a German Vocabulary Test (Wortschatztest; Schmidt and Metzler (1992)). Control subjects reported to have no neurological disorders or past or present psychiatric diseases. In addition, the time of day at which the EEG recording took place was matched pairwise between groups. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). They signed an informed consent form. All procedures followed the ethical guidelines of the Declaration of Helsinki.

Several post-hoc tests were performed to control for the effects of potential moderators. To assess the impact of comorbid depressive disorder, we splitted the patient group in patients with ($n$ = 9) and without comorbid depression ($n$ = 11). Medication effects were evaluated by splitting the patient group in a medicated group ($n$ = 13) and an unmedicated group (n = 7).

**Stimuli and procedures**

Three different types of auditory stimuli were presented. High-pitched tones (1000 Hz) were used as targets, low-pitched tones (700 Hz) as standards, and nonrecurring complex sounds (described in Fabiani and Friedman (1995)) as novel

events. The novel sounds included animal, environmental and synthesized sounds. Target and standard tones had the duration of 336 ms. The duration of the novel sounds ranged between 159 ms and 399 ms (mean 336 ms). All auditory stimuli were delivered via loudspeakers at 75 dB SPL.

**Task**

The novelty oddball task consisted of nine blocks with short breaks in-between. The first block included 100 stimuli with 12 targets *(p* = 0.12) and 88 standards *(p* = 0.88), but no novels, served as a practice block. Each of the other blocks included eight novels *(p* = 0.12), 8 targets (p = 0.12) and 64 standard stimuli *(p* = 0.76). The stimuli were presented in a pseudo-randomised order with an interstimulus interval of 1.0 seconds. At least two standard stimuli followed after each novel and target stimulus. Subjects were instructed to press a key as fast and accurate as possible when the target tone appeared and to minimize head and eye movements during the test blocks.

**EEG recording**

The electroencephalogram (EEG) and the electrooculogram (EOG) were recorded from 64 electrode sites using a *BrainAmp* EEG amplifier and *BrainVision* Recorder software (Brainproducts, Munich, Germany). An *EasyCap* electrode cap system (Falk Minow Services, Munich, Germany) was employed, with electrodes placed concentrically. All electrode impedances were kept below 5 kΩ. The recordings were referenced to activity at Cz. Signals were digitized with a sampling rate of 500 Hz and amplified with a filter band pass of .01–100 Hz.

**Data Analysis**

EEG data were digitally filtered with a low-pass filter at 40 Hz. The EEG was then re-referenced off-line to average reference and corrected for eye movement artefacts using the multiple source eye correction method (MSEC; Berg and Scherg (1994) implemented in BESA (Brain Electrical Source Analysis, v 5.1, MEGIS Software GmbH, Gräfeling, Germany). Stimulus-locked epochs between 100 ms pre- and 1000 ms post-stimulus were extracted, and artefact-contaminated epochs were rejected. The 100 ms interval preceding stimulus onset served as baseline. Target and novel epochs were then separately averaged for each subject. The novelty P3 amplitude was defined as the mean amplitude in a 100-ms time window (250-350 ms) around the peak latency of the grand-average waveform at the electrode site with the highest peak amplitude (FCz). We analyzed the novelty P3 amplitude using an analysis of variance (ANOVA) with the between-subjects factor group (patients vs. controls), and the within-subjects factor electrode site (F1, Fz, F2, FC1, FCz, FC2, Cz, CP1, CPz, CP2, P1, Pz vs. P2). Greenhouse-Geisser correction was applied. Electrodes were selected in accordance with earlier studies (Friedman, Cycowicz, & Dziobek, 2003) and with visual inspection of topographic distribution of the P3 in the current experiment (figure1). Novelty P3 latency was individually measured at FCz, the electrode site with the largest amplitudes across subjects. An analogous process was implemented for the target P3 amplitude. It was measured as 100 ms mean amplitude around the peak latency at electrode site Pz in the grand average (380-480 ms). As target P3 amplitudes have a more posterior topography (Friedman, Cycowicz, & Gaeta, 2001; Ranganath & Rainer, 2003), two more electrodes (PO1/PO2) were included in the ANOVA. Target P3 latency was measured at Pz. We further conducted ANOVAs including the between-subject factors medication

(medicated vs. unmedicated patients) and comorbidity (current depression vs. no currend depression. Further, we looked for possible moderator variables by conducting the ANOVAs with the between-subjects factor gender and by correlating the novelty P3 (measured at FCz electrode site) and the target P3 (measured at Pz electrode site) with OCD illness severity (quantified with the YBOCS score).

## Results

### Behavioural performance

Overall performance was very high. There was no difference between groups regarding reaction times to targets, $t(38) = -0.82$, $p = .42$, number of omissions, $t(38) = -0.36$, $p = .72$, rate of false alarms to novels, $t(38) = -1.06$, $p = .29$, or standards, $t(38) = 1.69$, $p = .10$ (table 3)

### Event-related potentials

Group differences

There was no significant difference in the novelty P3 amplitude between the patient and the control group, $F(1,38) = 0.13$, $p = .90$ (Figure 2). The interaction Group x Electrode site was not significant, $F(12,38) = 0.80$, $p = .45$. Further, the novelty P3 latency did not differ between groups, $t(38) = -.69$, $p = .496$.

Furthermore, no significant differences were detected between the patient and the control group with respect to the target P3 amplitude, $F(1, 38) = 0.14$, $p = .71$. Again, there was no significant interaction of Group x Electrode site, $F(12, 38) = 0.30$, $p = .79$. Target P3 latency was not different between groups as well, $t(38) = 0.47$, $p = .64$.

Analyses of moderator variables

There was neither an effect of gender, medication or comorbid depression on the novelty P3 amplitude found in ANOVAs comparing different groups or in correlations between novelty P3 amplitude and scales measuring illness severity.

## Discussion

In this study, the hypothesis was tested if the orienting response to novel acoustic stimuli in an active attentional mode is altered in patients with OCD. Administering a novelty oddball paradigm, the novelty P3 amplitude in the event-related brain potential was used to examine the orienting response. An enhancement of the novelty P3 amplitudes could not be observed in patients with OCD compared to healthy control subjects. The results of this study combined with our earlier results (Ischebeck et al., 2011) state that novel stimuli induce heightened attention in patients with OCD only in passive but not in active attentional mode. The results are in line with an earlier study comparing novelty P3 in passive and active attentional conditions (Grillon & Ameli, 1994). They found enhanced novelty P3 amplitudes due to the anticipation of electric shocks only in passive attentional mode. We interpret the influence of the attentional conditions due to a higher sensitivity of the threat detection system to novel stimuli when they are not actively attended to. Another explanation for the differences between active and passive conditions stems from the results from (Friedman, Kazmerski, & Cycowicz, 1998). They found a reduction of the novelty P3 in a passive attentional mode compared to the novelty P3 in an active attentional mode in a group of healthy participants. Therefore, it might be that in passive attentional mode attention derives mainly from simple stimulus features, but in active attentional mode also require intentional processes (Schupp, Flaisch,

Stockburger, & Junghofer, 2006), which might override or interact with automatic processes (Chong et al., 2008). This leads to the assumption that the automatic novelty processing in OCD is enhanced, but it can only be observed in a passive attentional mode because different processes are involved in the active attentional mode.

The results differ from results of enhanced P3 amplitudes following distracting stimuli in other anxiety disorders in active attentional mode (Clark, McFarlane, Weber, & Battersby, 1996; Kimble et al., 2000). This might be due to an even more hypersensitive threat detection system in other anxiety disorders or lower active intentional control processes in these disorders. Other explanations for the differing findings may result from task related differences between studies. The study of Clark et al. (1996) used a three-tone oddball task with a distractor sound instead of novel sounds used in our study. Furthermore, the sounds were presented against a continuous background of 30 db SL white noise and the inter-stimulus interval was double sized. Therefore the choice of the sounds and the presentation might be important distinguishing attributes between the studies. Simons, Graham, Miles, and Chen (2001) argue that the P3 amplitude following novel stimuli does not differ from the P3 amplitude following other distracting sounds in healthy subjects. It might be different though in patients with anxiety disorders, as Kimble et al. (2000) found a relatively heightened P3 following novel sounds compared to a lower P3 following rare, repeated distracting sound in patients with a posttraumatic stress disorder compared to healthy control subjects.

Comparing the task of our study to the one of the study of Kimble et al. (2000) one notices that the novel stimuli in their study appeared in a lower frequency (7.5% vs. 12%). Even though Steiner, Brennan, Gonsalvez, and Barry (2013) found no

effect of the distance between two distractor sounds on the P3 following the distractor sounds, this might be different for novel stimuli, where it might lead to a pronounced importance of the novel stimuli. Other differences between the task in Kimble et al. (2000) and the task in our study point in the same differentiation between these studies. There was a slightly louder presentation of the sounds (80 db vs. 75 db) and a presentation of a three-tone oddball task before the novelty oddball task in the study of Kimble et al. (2000). These differences might pronounce the importance of the novel sounds which could make them more activating for the threat detection system. This could lead to a heightened novelty P3 in anxiety patients even when the sounds are presented in active attentional mode.

There are some limitations of this study. The patient sample included a high proportion of patients taking medication and/or having comorbid depressive disorder. These factors were controlled statistically with no significant differences found. Thus, neither depressive symptoms nor medication appear to be determinants of the finding. Nevertheless, it is highly desirable to examine a larger sample of monomorbid and medication-free OCD patients to confirm the present results.

To conclude, the results of the present study suggest that the cortical orienting response to acoustic novel stimuli in OCD patients does not differ from healthy control subjects in active attentional mode. Considering the finding of a heightened cortical orienting response to acoustic novel stimuli in OCD patients in passive attentional mode (Ischebeck et al., 2011), further studies should investigate these differences in novelty processing in OCD patients due to attentional mode and elucidate the underlying processes.

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## Tables

Table 1: Age at illness onset, comorbidity and medication of OCD patients.

| Patient no. | Age at illness onset (years) | Comorbid disorders | Medication |
|---|---|---|---|
| 1 | 10 | None | Reboxetine |
| 2 | 15 | Panic disorder with agoraphobia (300.21) | Fluvoxamine |
| 3 | 30 | None | None |
| 4 | 5 | Panic disorder without agoraphobia (300.01) | None |
| 5 | 22 | None | None |
| 6 | 17 | None | Fluoxetine |
| 7 | 28 | Social phobia (300.23) | Paroxetine |
| 8 | 30 | Major depressive disorder, single episode (296.21) | Paroxetine |
| 9 | 20 | None | Fluoxetine |
| 10 | 28 | Major depressive disorder, recurrent (296.31); not otherwise specific eating disorder (307.50) | Citalopram |
| 11 | 10 | Major depressive disorder, single episode (296.22) | None |
| 12 | 19 | None | Fluvoxamine + Doxepin |
| 13 | 8 | None | None |
| 14 | 9 | Major depressive disorder, recurrent (296.35) | Fluoxetine |
| 15 | 20 | None | Clomipramine |
| 16 | 27 | Major depressive disorder, recurrent (296.31) | Fluoxetine + Trimipramine |
| 17 | 7 | None | None |
| 18 | 16 | None | Paroxetine |
| 19 | 19 | Major depressive disorder, recurrent (296.31) | Paroxetine |
| 20 | 16 | Dysthymic disorder (300.4); undifferentiated somatoform disorder (300.82) | None |

Table 2: Socio-demographic and clinical characteristics of OCD patients and healthy control subjects. Numbers, means and standard deviations (in parentheses) are reported.

| | Healthy Controls | OCD patients |
|---|---|---|
| N | 20 | 20 |
| Sex (Males/Females) | 10/10 | 10/10 |
| Age (years) | 34.1 (9.2) | 33.8 (9.0) |
| Years of education | 11.7 (1.6) | 11.4 (1.4) |
| Verbal IQ | 110.0 (10.3) | 106.7 (8.7) |
| Yale-Brown Obsessive-Compulsive Scale (YBOCS) | -- | 18.3 (6.3) |
| Obsessive-Compulsive Inventory (OCI-R) | 6.9 (4.0) | 28.7 (13.1) |
| Montgomery Asberg Depression Scale (MADRS) | -- | 10.35 (6.9) |
| Beck Depression Inventory (BDI) | 2.2 (2.5) | 13.2 (7.6) |

Table 3: Reaction time to targets, number of misses, incorrect reactions to novels and to standards in OCD patients and healthy control subjects (group means and standard deviations).

| | Healthy controls | OCD patients |
|---|---|---|
| Mean reaction time (ms) | 432 (78) | 443 (93) |
| Misses | 0.7 (1.2) | 0.9 (1.4) |
| Incorrect reactions to novels | 0.5 (0.9) | 0.3 (0.4) |
| Incorrect reactions to standards | 0.2 (0.4) | 2.0 (4.6) |

**Figure captions**

Figure 1. Topographical ERP scalp distribution maps (equidistant projection 90°) of the target P3 (380-480ms) and the novelty P3 (250-350ms).

Figure 2. Grand-average ERP-Waveforms of novel stimuli of OCD patients and healthy controls. Midline Electrodes are depicted.

**Figures**

Figure 1:

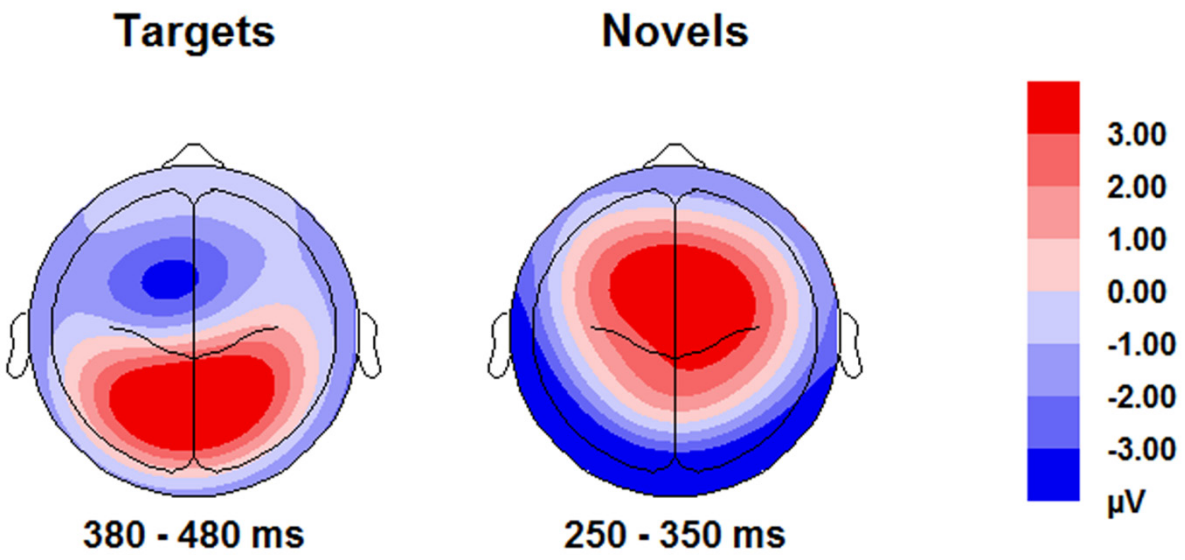
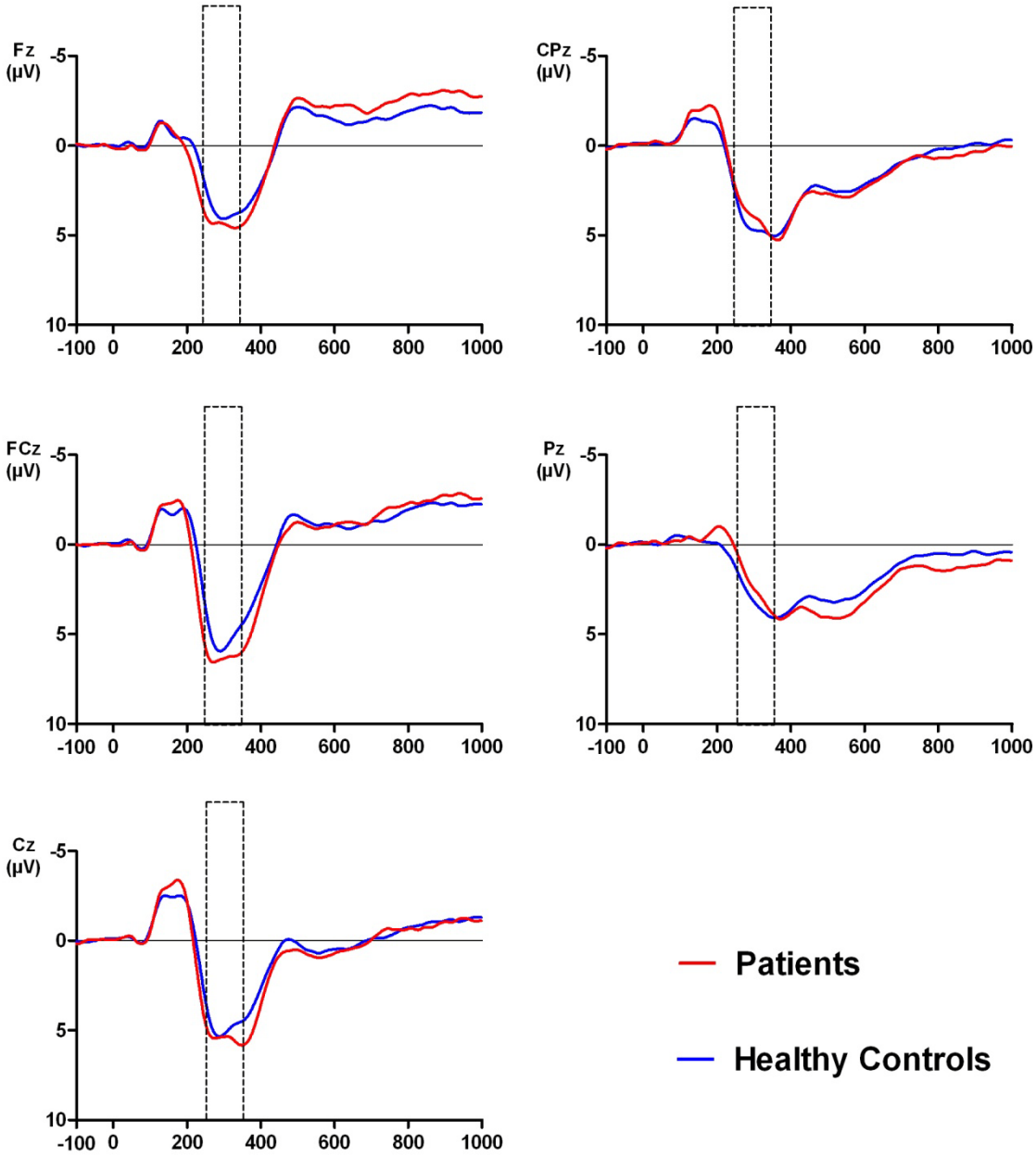


Figure 2:


Fz
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-100
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200
400
600
800
1000
Patients
Healthy Controls

# Frontal EEG asymmetry in obsessive-compulsive disorder

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**Abstract**

Hemispheric asymmetry of alpha band power in the electroencephalogram (EEG) has been linked to approach/avoidance motivation and may index the risk for anxiety disorders and depression. Alpha asymmetry has not yet been thoroughly investigated in obsessive-compulsive disorder (OCD). We quantified lower alpha band power (8-10 Hz) as well as upper alpha band, theta, and beta band power at frontal and parietal electrodes in 18 OCD patients and 18 matched healthy controls during blocks of rest and presentation of neutral, aversive, and OCD-related pictures. Patients showed a relative shift of frontal alpha activity in the 8-10 Hz band to the left hemisphere across all conditions. This shift was not observed over parietal areas, and also did not show in the upper alpha, and the theta and beta bands. Aversive pictures induced a left-shift in both groups relative to all other conditions. Altered hemispheric distribution of lower alpha band activity supports the hypothesis of relatively increased avoidance motivation in OCD. Unlike in other anxiety disorders, altered asymmetry was not confined to conditions evoking negative emotions. Instead, it appears to be more trait-like in OCD, suggesting a link to depression.

## Introduction

Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by high levels of distress evoked by intrusive and recurring thoughts, referred to as obsessions, frequently accompanied by ritualized and repeated behaviours or mental acts, i.e. compulsions, which are attempts to reduce the distress. Similar to other anxiety disorders, avoidance behaviour is a core clinical feature of OCD (Bartz & Hollander, 2006; Leckman et al., 2010). In brain imaging studies, OCD patients have shown greater reactivity to negative stimuli (Schienle, Schafer, Stark, Walter, & Vaitl, 2005; Simon, Kaufmann, Musch, Kischkel, & Kathmann, 2010). Such results suggest altered emotion processing in OCD. The two cerebral hemispheres have been proposed to be differentially engaged in emotion processing (Davidson, 1995). Accordingly, relatively greater left frontal brain activity points to the activation of the approach system, while greater right frontal brain activity reflects the activation of the withdrawal system (Davidson, 1995, 1998). Asymmetry of frontal brain activity can be assessed with electroencephalographic (EEG) measures. Alpha power asymmetry has been used to test relative activation of both hemispheres, whereby alpha power is inversely related to brain activation (Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Laufs et al., 2003). Consequently, relative lower left frontal alpha power indicates dominance of the approach-related emotion system, while relative lower right frontal alpha power reflects dominance of the withdrawal-related emotion system. The present study aims at investigating anterior alpha asymmetry in OCD patients during rest and while viewing emotional pictures.

It has been proposed (Davidson, 1993, 1998) that individuals with a dominant avoidance style are more vulnerable to internalizing disorders. In line with this hypothesis lower right than left frontal alpha scores were found in non-clinical samples of high anxious in comparison to low-anxious subjects (Mathersul, Williams,

Hopkinson, & Kemp, 2008). Alpha asymmetry also predicted trait anxiety one year later (Blackhart, Minnix, & Kline, 2006). Furthermore, altered alpha asymmetry has been shown in patients with a panic disorder (Wiedemann et al., 1999; Wise, McFarlane, Clark, & Battersby, 2011), social phobia (Davidson, Marshall, Tomarken, & Henriques, 2000; Moscovitch et al., 2011) posttraumatic stress disorder (Rabe, Beauducel, Zollner, Maercker, & Karl, 2006), and depression with (Bruder et al., 1997) and without (Allen & Kline, 2004; Henriques & Davidson, 1991; Kemp et al., 2010) co-morbid anxiety disorder. Studies in OCD patients are scarce as yet, with inconsistent results. While Kuskowski et al. (1993) found a shift of alpha power to the left hemisphere in 13 patients compared to 10 controls, Tot et al. (2002) reported smaller alpha power scores over left frontal scalp electrodes but failed to describe methodological details. Also, they referred to relative power scores, instead of using absolute power of each band as common in the EEG asymmetry literature. Another study found no difference in alpha asymmetry (Bucci et al., 2004). The inconclusive evidence, the lacking consideration of state variables as well as methodological limitations of the previous studies motivate further research on this issue.

Alpha asymmetries turned out to be driven by both trait and state factors (Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005; Hagemann, Naumann, Thayer, & Bartussek, 2002). State-related influences on alpha asymmetry have been shown in healthy individuals with high trait anxiety (Crost, Pauls, & Wacker, 2008; Lewis, Weekes, & Wang, 2007), and in patients diagnosed with anxiety disorders (Davidson et al., 2000). Picture stimuli have been used to reliably evoke emotional responses that can be measured as changes of alpha asymmetry (Huster, Stevens, Gerlach, & Rist, 2009). Patients suffering from panic disorder showed a significant shift of alpha power to the left after the presentation of panic-relevant and panic-irrelevant negative pictures that was larger than that seen in healthy control subjects

(Wiedemann et al., 1999). Similarly, patients with posttraumatic stress disorder showed lower right frontal alpha power compared to left frontal alpha power during viewing trauma-related pictures but not during viewing neutral or positive pictures (Rabe et al., 2006). These studies suggest that alpha asymmetry in high anxious individuals and seemingly even more in patients with anxiety disorders is moderated by emotions induced by the actual situation.

In the present study we investigated frontal alpha asymmetry in OCD patients and in healthy control subjects during a resting condition and while they were viewing neutral, negative and OCD-related pictures. Since previous findings indicate that effects of emotion are more pronounced in the lower alpha band (Davidson et al., 2000; Wacker, Heldmann, & Stemmler, 2003), and the lower alpha band has also been shown to be more strongly related to cortical activity (Oakes et al., 2004), we used the 8-10 Hz band as our primary target variable. To check whether group-specific asymmetry effects can also be observed in other frequency bands, we additionally assessed upper alpha band (10,5-12,5 Hz), as well as theta (4-7,5) and beta band power (13–30 Hz) to specify any between-group differences. Furthermore, hemispheric effects were analyzed both from frontal and from parietal electrode sites. Affective pictures were presented to examine changes of EEG asymmetry associated with emotional states. Based on previous findings in anxiety disorders, a relative shift of alpha power at frontal scalp sites to the left was expected in OCD patients when negative or OCD-related pictures are presented. Negative pictures should elicit a left-shift of alpha also in the control group but this effect should be stronger in patients. OCD-related pictures, however, should pronounce alpha asymmetry in the patient group only.

## Materials and Methods

### *Participants*

Twenty-one OCD patients (8 males, 13 females) were enrolled in the study. For analysis, data of 18 patients could be used after excluding data of three patients due to excessive artefact contamination. Patients were recruited from the outpatient clinic of the Department of Psychology at Humboldt-Universität zu Berlin. OCD diagnosis was based on DSM-IV criteria (American Psychiatric Association, 1994) verified by the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Gibbon, Hilsenroth, & Segal, 2004). Exclusion criteria were the presence of neurological disorders, previous or current psychotic symptoms, or substance related disorders. OCD was the primary diagnosis in all patients, while seven patients had comorbid diagnoses (table 1). All patients received cognitive-behavioural psychotherapy, and 9 patients were additionally taking psychotropic medication at the time of study participation (6 took selective serotonin reuptake inhibitors, and 3 took clomipramine). OCD symptoms were assessed in both groups using the Obsessive-Compulsive Inventory Revised (OCI-R; Foa et al., 2002). Severity of OCD was rated by a trained clinician using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). Affective symptoms were assessed in both groups using the Beck-Depression-Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and in patients only, by the Montgomery-Asberg-Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). The MADRS was again administered by trained clinicians. State and trait anxiety were measured with the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). German versions of the scales were used. On average, patients had moderate OCD symptoms, mild depressive symptoms and slightly enhanced trait and state anxiety scores (table 2).

Twenty-one control participants were matched to the OCD patients with respect to gender, age, and education. Data of 18 control participants could be used after excluding data of three control participants due to excessive artefact contamination (table 2). Control participants were screened using a questionnaire based on DSM-IV criteria. No control participant showed past or present signs of a mental disorder. Verbal intelligence was assessed using a German Vocabulary Test (Schmidt & Metzler, 1992). All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). They provided written informed consent to the study. The protocol was approved by the ethical review board of the Charité, University Medicine Berlin.

*Task*

During a passive viewing task six pictures were presented (2 neutral, 2 negative and 2 OCD-related). Each picture was presented for one minute preceded by a fixation cross displayed for one minute. EEG recordings were made during picture presentation and during fixation. Participants were instructed to fixate the cross or to look at the pictures. They had no further task. After the end of each picture presentation participants were requested to rate the picture regarding arousal, dominance and unpleasantness using a paper-and-pencil version of the Self-Assessment Manikin (SAM, Bradley & Lang, 1994). Patients were additionally asked to rate the intensity of their obsessions and compulsive urges while viewing the pictures. Pictures were always presented in the same order (neutral, OCD-related, negative, neutral, OCD-related, negative) but the starting picture systematically differed across subjects. Thus, each picture appeared with the same frequency at any position.

Negative and neutral pictures were taken from the International Affective Picture System (IAPS, Lang, Bradley, & Cuthbert, 2005). The IAPS identification numbers were 2703 and 2800 for the negative pictures and 7000 and 7041 for the neutral pictures. OCD-related pictures were selected from the stimulus set developed by Simon et al. (2010). These pictures were individually selected according to the patients' specific symptoms, and informed by their psychotherapist's advice. Thus, each control participant was presented with the identical stimuli as his/her respective matched patient.

*EEG recording*

The electroencephalogram (EEG) was recorded from 64 electrode sites using a *BrainAmp* EEG amplifier and *BrainVision* Recorder software (Brainproducts, Munich, Germany). An *EasyCap* electrode system (Falk Minow Services, Munich, Germany) was employed with electrodes placed concentrically. Electrode impedances were kept below 5 kΩ. Recordings were referenced to Cz. Signals were digitized with a sampling rate of 500 Hz and amplified with a high pass filter of .01 Hz.

*Data Analysis*

Ratings of arousal, dominance, valence and evoked OCD symptoms were averaged for each picture type. ANOVAs were conducted for each rating dimension with the between-subjects factor group (patients, controls) and the within-subjects factor picture type (neutral, negative, OCD-related) followed by pair-wise contrasts between picture types. The ANOVA for ratings of evoked OCD symptoms was conducted for the patient group only.

The EEG was then re-referenced off-line to the average of all EEG leads (AVR), and split into 1-minute blocks. Then, from each block 119 epochs of 2.048-s length were extracted that overlapped by 1.5 s. Epochs were first visually inspected to remove epochs with gross artefacts. A computer-based algorithm was used to detect blinks and other ocular artefacts. Those epochs were excluded from further analysis. On average 57.4% of the epochs were kept in the analyses, with no significant differences between groups (resting condition: $t(38) = 1.83$; neutral condition $t(38) = 1.52$; negative condition $t(38) = 1.00$; OCD-related condition $t(38) = 1.54$; all $p > .05$). Six participants (3 patients, 3 controls) were excluded due to excessive artefact contamination (< 15% of artefact-free data in the resting EEG condition). Artefact-free data were analyzed using Fast Fourier transformation (FFT) with a Hamming window (50% taper) to estimate power in different frequency bands (Towers & Allen, 2009). Lower alpha band power was determined from 8 to 10 Hz band. We further assessed upper alpha (10,5-12,5 Hz), theta (4-7,5) and beta power (13–30 Hz) to test whether effects in the lower alpha band are frequency-specific. Power values of the epochs were separately averaged for the resting condition, and for negative, neural, and OCD-related picture conditions. Resulting mean power values were logarithmized (ln) to approximate normal distribution.

Power in all bands was then statistically analyzed using ANOVA with the between-subjects factor group (patients, controls) and the within-subjects factors condition (resting, neutral, negative, OCD-related) and hemisphere (left, right). To enhance reliability, values from the six left frontal electrodes (F1, F5, FC1, FC3, FC5, AF3) were averaged. Analogously, right frontal electrodes were averaged (F2, F6, FC2, FC4, FC6, AF4). To control whether asymmetry effects were specific to frontal scalp sites, power in different frequency bands was also computed from parietal scalp sites. To this end values from six left parietal electrodes (P1, PO3, P7, PO1

CP3, CP5), and six right parietal electrodes (P2, PO4, P8, PO2, CP4, CP6) were averaged, respectively.

## Results

### *Picture ratings*

Arousal, valence and dominance ratings showed a main effect of picture type, $F(2,68) = 59.95$, $p < .001$; $F(2,68) = 59.11$, $p < .001$; $F(2,68) = 35.57$, $p < .001$, respectively. Pair-wise comparisons revealed that ratings of arousal, unpleasantness and dominance were each lower for neutral than for OCD-related and negative pictures, and for OCD-related than for negative pictures (all $p < .01$). A significant main effect or interaction of Group was not found. Evoked OCD symptom ratings also showed a main effect of picture type, $F(2,34) = 14.98$, $p < .001$, which was due to higher scores for OCD-related compared to neutral ($p < .001$) and negative pictures ($p < .05$), and for negative compared to neutral pictures ($p < .01$).

### *EEG measures*

Over anterior regions, a difference in hemispheric distribution between groups was revealed by a significant group by hemisphere interaction, $F(1,34) = 9.00$, $p = .005$ (see figures 1 and 2). Post hoc analyses within each group showed that in patients a left-lateralized alpha distribution (factor hemisphere) could be observed, $F(1,17) = 5.42$, $p = .026$, whereas in controls a trend towards a right-lateralized alpha distribution was found, $F(1,17) = 3.67$, $p = .064$. Further comparisons within each hemisphere did not reveal significant main effects of group in either the left, $F(1,) = 0.82$, $p = .373$, or the right hemisphere, $F(1,34) = 0.16$, $p = .696$, suggesting that the interaction resulted from non-significant deviances of opposite directions in left and right hemispheres, rather than from one hemisphere alone.

Condition showed a main effect on 8-10 Hz alpha power, $F(3,32) = 9.52$, $p < .001$, and brain asymmetry differences between conditions were indicated by a significant interaction of condition by hemisphere, $F(2,32) = 4.19$, $p = .009$. Post-hoc contrasts revealed shifts towards more left-sided alpha during the negative condition compared to rest, $F(1,34) = 4.50$, $p = .041$, to neutral, $F(1,34) = 4.46$, $p = .042$, and to OCD-related conditions, $F(1,34) = 10.31$, $p = .003$ (see figure 3). Further post-hoc comparisons showed that the main effect of condition was due to higher alpha power for resting and neutral than OCD-related pictures (all $p < .01$) and resting than negative pictures (all $p < .05$), in both hemispheres and groups. There were neither a significant main effect of group nor significant interactions between group and condition, or between group, condition and hemisphere (all $p > .20$). To address the question whether the effects were specific to anterior brain regions, the analyses were repeated with data from posterior electrodes. There were no significant brain asymmetry differences neither between groups, $F(1,34) = .037$, $p = .55$, nor conditions, $F(2,32) = 1.82$, $p = .15$, in posterior regions.

Furthermore, the frequency-specificity of the anterior asymmetry changes in OCD patients was controlled by doing analog tests in the upper alpha, the theta, and the beta band. We did not find either a significant main effect of group nor significant interactions between group and hemisphere, or group and condition, or between group, condition and hemisphere (all $p > .20$) in the upper alpha band. However, there was a main effect of condition, $F(3,32) = 3.37$, $p = .030$, and a significant interaction of condition by hemisphere, $F(2,32) = 4.78$, $p = .009$. Post-hoc contrasts suggested more upper alpha activity in the resting than in the OCD-related condition and a shift towards a more left-sided alpha during the negative condition.

In the theta band a nonsignificant trend towards an interaction between group and hemisphere, $F(1,34) = 3.69$, $p = .063$ was seen. There was also a main effect of

condition, $F(3,32) = 6.48$, $p = .001$. Post hoc tests revealed that the main effect of condition was due to lower theta power in the resting condition than during viewing neutral and negative pictures. No main effect of group nor significant interactions between group and condition, or between group, condition and hemisphere (all $p > .20$) were found.

In the beta band, the main effect of group showed a trend towards more beta in patients, $F(1,34) = 3.28$, $p = .079$. We further observed a nonsignificant trend towards an interaction between group and condition, $F(,) = 2.70$, $p = .069$. There were neither significant interactions between group and hemisphere, nor between group, condition and hemisphere (all $p > .10$).

## Discussion

The present study analyzed brain asymmetry as measured with EEG power measures over frontal scalp areas. We were primarily interested in differences of this measure between OCD patients and healthy control participants in the lower alpha band. To relate alterations to specific conditions, a resting condition, as well as picture viewing conditions were applied, with pictures showing either neutral scenes or objects, pictures eliciting negative affect, or pictures potentially provoking mild OCD symptoms. It was hypothesized that OCD patients show more left-shifted frontal alpha, probably limited to the presentation of negative and OCD-related pictures. Results revealed that patients in fact show a relative shift of lower alpha activity to left frontal brain regions which means reduced dominance of left-sided brain activation across all conditions. Across groups, viewing negative pictures leads to a relative left-shift of alpha power (i.e. decrease of left frontal brain activation) compared to all

remaining conditions. However, there was no interaction of this effect with diagnostic status.

Interestingly, the relative shift of EEG power was specific to frontal areas and also to the lower alpha band, with a trend still seen in the theta band.

The relative shift of 8-10 Hz alpha power to the left hemisphere in OCD patients is interpreted to indicate more weight for the withdrawal-avoidance mode relative to the approach mode of the motivational brain system in OCD patients (Davidson, 1998). Greater resting alpha asymmetry is in line with one previous finding in OCD patients (Kuskowski et al., 1993; Tot et al., 2002) but conflicting with another one (Bucci et al., 2004). Relatively greater activation of the withdrawal-avoidance system has been proposed to be a risk indicator for internalizing disorders. It was found in other internalizing disorders either due to enhanced activity of the withdrawal system (Bruder et al., 1997; Kuskowski et al., 1993; Wiedemann et al., 1999), or reduced activity of the approach system (Henriques & Davidson, 1991; Kemp et al., 2010; Tot et al., 2002). In the present study, altered asymmetry in OCD patients was not solely attributable to more activity of the withdrawal system or less activity of the approach system. Rather, it appears that both systems contribute to the deviance.

Altered asymmetry of lower alpha band activity in OCD was not confined to the resting condition but could also be observed during passive viewing of affective pictures. Group differences of asymmetry were robust across all conditions and picture types. The finding of trait-like group differences independent of condition effects is in line with our previous study showing that OCD patients have enhanced cortical orienting responses towards novel stimuli, a deviance that was independent of emotional context (Ischebeck, Endrass, Simon, & Kathmann, 2011). Further, it is also consistent with the finding that OCD patients show larger amplitudes and shorter

latencies of their startle response independent of the emotional content of a film they watched, although both groups had more pronounced startle responses for negative affective film clips (Kumari, Kaviani, Raven, Gray, & Checkley, 2001).

Both groups showed experimentally induced shifts of alpha power to the left when pictures evoking negative affect were presented. This finding is in line with a previous study using IAPS pictures (Huster et al., 2009). Against expectation, OCD-related pictures were not effective in provoking asymmetry shifts in patients. This might be due to the specifics of the standardized experimental situation which ameliorates responsibility feelings and discomfort of OCD patients, thus making the OCD-related pictures less threatening.

Interestingly, diagnosis-related alterations independent of emotional state manipulation have also been observed in depressive patients (Stewart, Coan, Towers, & Allen, 2011), whereas anxiety disorder patients show a relative left-shift of alpha EEG only in specific situations (Davidson et al., 2000; Rabe et al., 2006; Shankman et al., 2008). On the basis of these findings it is tempting to conclude that OCD shows more relationship to depression than to the anxiety disorders regarding the trait-like character of brain asymmetry. A constantly enhanced role of the withdrawal-avoidance system for the regulation of emotions and motivation is also in accord with the high risk of comorbid affective disorders in OCD (Ruscio, Stein, Chiu, & Kessler, 2010). Moreover, OCD patients were shown to score high on work and activity impairment items of the Hamilton Depression Rating Scale, and this might reflect the relatively weakened role of the approach system (Moritz, Meier, Hand, Schick, & Jahn, 2004). The main finding of relatively enhanced activity of the withdrawal-avoidance system in OCD patients is also in accordance with higher harm avoidance questionnaire scores (Ettelt et al., 2008; Lyoo, Lee, Kim, Kong, & Kwon,

2001), and with enhanced avoidance learning in a probabilistic learning task (Endrass, Kloft, Kaufmann, & Kathmann, 2011).

Frontal brain asymmetry measures may also have clinical relevance. There is some evidence that alpha asymmetry is predictive of treatment outcome. A relative right-shift of alpha EEG was found in patients with a diagnosis of major depression responding to treatment with selective serotonine reuptake inhibitors (Bruder et al., 2008; Bruder et al., 2001). In contrast, patients with social anxiety disorder showed symptom reductions that were positively correlated with the amount of pre-treatment left dominance of alpha (Moscovitch et al., 2011). Although more research is necessary to corroborate alpha asymmetry scores as predictors of treatment outcome, this might be a promising application.

An even more challenging aim for brain asymmetry research is the direct modification of trait-like asymmetry persisting for longer periods of time. Thereby, in case of success one might modulate the relative effects of the approach and the withdrawal system. Neurofeedback training was used to enhance right alpha power in healthy subjects (Allen, Harmon-Jones, & Cavender, 2001), and in depressive patients (Choi et al., 2011). Of note, the successful change of alpha asymmetry had significant effects on reducing depressive symptoms, as well as on self-reported and objective indicators of emotion. Another intervention which is promising in changing alpha asymmetry towards a more right-sided distribution is mindfulness meditation (Barnhofer et al., 2007; Davidson et al., 2003). Finally, cognitive behaviour therapy led to a reduction of left-sided asymmetry in patients suffering from posttraumatic stress disorder (Rabe, Zoellner, Beauducel, Maercker, & Karl, 2008), and in patients with social anxiety disorder (Moscovitch et al., 2011). Research on alpha asymmetry as a treatment target is still in its beginning, but merits further consideration.

There are some limitations of the current study that should be discussed. First, a subgroup of patients was receiving pharmacological treatment during study participation. However, additional analyses to estimate the effects of medication revealed neither a main effect of medication nor interactions of medication with hemisphere or condition. Effect sizes ($eta^2$) for the critical hemisphere x group effect were similar for medicated ($eta^2$ = .23) and unmedicated patients ($eta^2$ = .19). So, it is unlikely that the core findings of the present experiment are biased by medication. Second, several patients had comorbid disorders, including major depression and social phobia. We reanalyzed the group x hemisphere interaction separately for co-morbid and mono-morbid patients. Again, no significant effect of this possible confounder was detected, although the effect size of the hemisphere x group interaction was larger for the mono-morbid compared to the comorbid subgroup of patients ($eta^2$ = .27 vs. $eta^2$ = .14). This means that the relative left-shift of alpha EEG in OCD patients is not due to comorbidity. Finally, the selection of pictures might have been suboptimal for the detection of altered asymmetry specific for OCD-related affective stimuli. Although the stimuli were individually selected for each patient based on the diagnostic records, a selection on the basis of actual picture ratings (Simon et al., 2010) by each patient might be more powerful in inducing specific effects. Future studies should include such selection procedures.

In summary, a shift of brain activation to relatively more right frontal activation as indicated by changed alpha power in the 8-10 Hz range was found in OCD patients compared to matched healthy control participants. This deviance was present independent of emotional stimulation. The finding is in accordance with the hypothesis of altered emotion processing in OCD patients characterized by a relatively stronger impact of the withdrawal-avoidance system. OCD patients share this characteristic with depressive patients whereas many anxiety disorders show

asymmetry alterations only in disease-relevant situations. Follow-up studies should clarify the predictive value of the asymmetry change.

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**Tables**

Table 1: Age at illness onset, comorbidity and medication of OCD patients.

| Patient no. | Years of Illness | Comorbid disorders | Medication |
|---|---|---|---|
| 1 | 15 | None | None |
| 2 | 8 | None | None |
| 3 | 12 | Major depressive affective disorder recurrent episode in full remission (296.36) | None |
| 4 | 10 | None | None |
| 5 | 4 | None | None |
| 6 | 31 | None | None |
| 7 | 3 | None | Citalopram |
| 8 | 16 | None | Escitalopram |
| 9 | 24 | Major depressive affective disorder recurrent episode in full remission (296.36) | Paroxetine |
| 10 | 24 | Major depressive affective disorder single episode mild degree (296.21) | Clomipramine |
| 11 | 22 | Anorexia nervosa (307.1), Major depressive affective disorder recurrent episode in partial or unspecified remission (296.35) | Citalopram |
| 12 | 4 | None | Fluoxetine |
| 13 | 20 | None | None |
| 14 | 36 | None | Escitalopram |
| 15 | 18 | Major depressive affective disorder single episode mild degree (296.21) | None |
| 16 | 17 | Social phobia (300.23) | None |
| 17 | 26 | Social phobia (300.23) | Clomipramine |
| 18 | 12 | None | Clomipramine |

Table 2: Socio-demographic and clinical characteristics of the analysis sample (18 OCD patients and 18 matched healthy control subjects). Means, standard deviations (in parentheses) and significant differences between groups are reported.

| | Healthy controls | OCD patients | *p* |
|---|---|---|---|
| N | 18 | 18 | |
| Gender (n males/ n females) | 7/11 | 7/11 | |
| Age (years) | 32.6 (10.0) | 33.3 (9.1) | n.s. |
| Years of education | 12.4 (1.2) | 12.4 (1.2) | n.s. |
| Verbal IQ | 110.6 (8.9) | 108.2 (8.7) | n.s. |
| YBOCS | -- | 19.6 (5.8) | |
| OCI-R | 7.1 (6.0) | 28.3 (13.5) | < .001 |
| MADRS | -- | 12.3 (10.3) | |
| BDI | 2.9 (3.3) | 12.7 (9.7) | = .001 |
| STAI–T | 34.1 (8.8) | 48.4 (10.5) | < .001 |
| STAI–S | 33.1 (6.3) | 40.1 (9.6) | = .015 |

Abbreviations: Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory-Revised; MADRS, Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory; STAI-T, Trait version of State-Trait Anxiety Inventory; STAI-S, State version of State-Trait Anxiety Inventory.

**Figure captions**

Figure 1. Topographical scalp distribution map (equidistant projection 90°) of group differences (controls, patients) in lower alpha power (8 -10 Hz).

Figure 2. Mean frontal alpha power (and standard errors) in the 8 - 10 Hz band, averaged across conditions (rest, neutral pictures, negative pictures, OCD-related pictures) and electrodes, broken down by groups and hemispheres.

Figure 3. Mean frontal alpha power (and standard errors) in the 8 - 10 Hz band, averaged across groups and electrodes, broken down by condition and hemisphere.

Figure 1

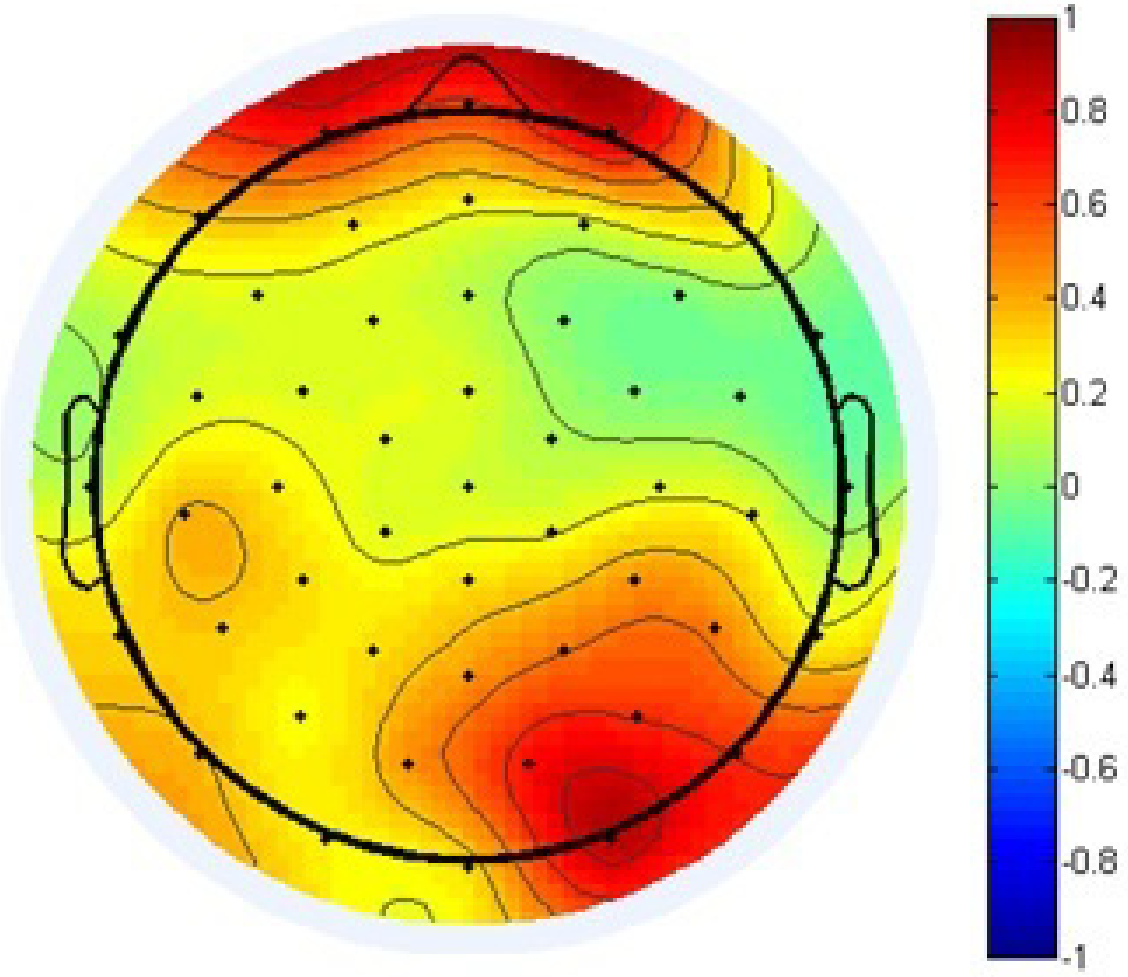


Figure 2

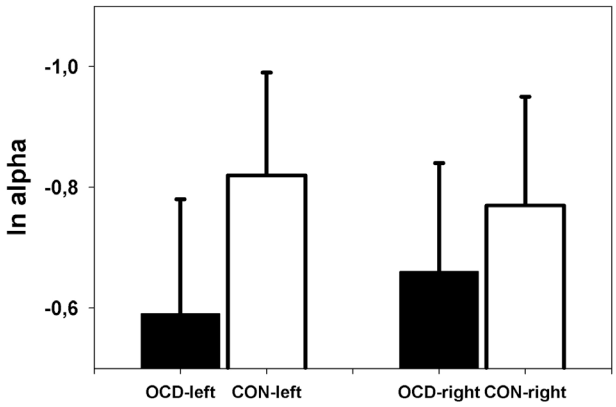
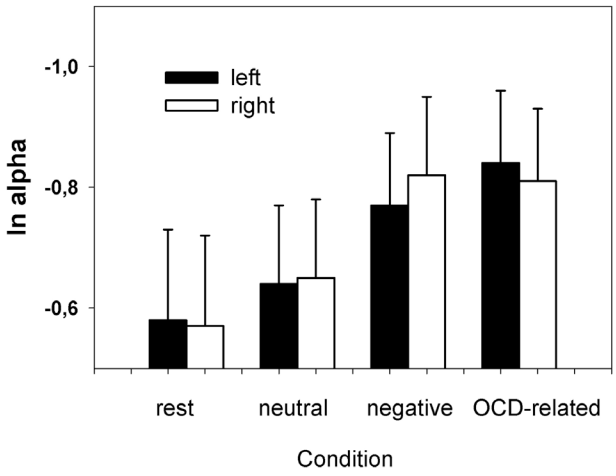


Figure 3:


-1,0
-0,8
-0,6
ln alpha
left
right
rest
neutral
negative
OCD-related
Condition

**Eidesstattliche Erklärung**

Hiermit erkläre ich an Eides statt,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
- dass diese Dissertation zum ersten Mal eingereicht wird,
- dass ich mich nicht anderwärts um den Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach besitze, und
- dass ich die zugrundliegende Promotionsordnung vom 03. August 2006 kenne.

Berlin, den 04. September 2013. Moritz Ischebeck