Endophänotypen der Zwangsstörung

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Zusammenfassung

Die Zwangsstörung ist eine komplexe psychiatrische Erkrankung, die durch intrusive Zwangsgedanken und repetitive Zwangshandlungen gekennzeichnet ist. Ihre Pathophysiologie umfasst insbesondere Dysfunktionen der cortico-striato-thalamo-corticalen Schleifen, die sich in exekutiven Funktionsdefiziten niederschlagen. Eine hohe Erblichkeit von etwa 50 % gilt als gut belegt; welche konkreten Gene zur Ätiologie der Zwangsstörung beitragen, ist jedoch weitgehend unklar. Eine Erleichterung der Identifikation von Risikogenen erhofft man sich durch die Untersuchung von Endophänotypen, da sie in Bezug auf genetische Ursachenanteile eine höhere ätiologische Spezifität aufweisen sollten als der klinisch sehr heterogene Phänotyp der Zwangsstörung. Endophänotypen sind quantitative störungsassoziierte Auffälligkeiten, die sowohl bei Patienten als auch bei deren genetisch Verwandten zu beobachten sind. In der vorliegenden Dissertation, der fünf Originalarbeiten zugrunde liegen, wurden verschiedene Endophänotypenkandidaten anhand einer der bislang größten tief phänotypisierten Stichproben von Zwangspatienten (n = ~ 200), deren nicht affizierten Angehörigen ersten Grades (n = ~ 100) und gesunden Kontrollprobanden (n = ~ 200) untersucht. Sämtliche Daten wurden im Rahmen der bizentrischen Studie „Neurokognitive Endophänotypen der Zwangsstörung und deren Hirnkorrelate“ erhoben und schließen ein strukturiertes klinisches Interview, verschiedene okulomotorische und neuropsychologische Testungen sowie ein elaboriertes Fragebogenpaket mit ein. Die hier analysierten Endophänotypenkandidaten umfassen die Ausführung von Antisakkaden, volitionalen Sakkaden und glatten Augenfolgebewegungen (engl. smooth pursuit eye movements, SPEM), die Planungsfähigkeit in der Turm von London (TvL)-Aufgabe sowie die Persönlichkeitseigenschaften Schadensvermeidung und Schizotypie. Sowohl Zwangspatienten als auch deren erstgradige Angehörige zeigten verglichen mit Kontrollprobanden eine signifikant erhöhte Rate von Antisakkadenfehlern mit Expresssakkadenlatenz, eine erhöhte intrapersonelle Variabilität der Antisakkadenlatenzen, eine geringere Planungsgenauigkeit in der TvL-Aufgabe sowie erhöhte Werte hinsichtlich Schadensvermeidung und Schizotypie. Für die globale Antisakkadenfehlerrate und für die Antisakkadenlatenz ergaben sich nur bei Zwangspatienten moderate Auffälligkeiten, bei Angehörigen jedoch nicht. Die drei Gruppen unterschieden sich nicht signifikant bezüglich ihrer volitionalen Sakkadenlatenzen sowie ihrer kontinuierlichen und prädiktiven SPEM. Insgesamt stützen die Befunde die Rolle spezifischer Auffälligkeiten in der Antisakkadenperformanz, in der

Planungsfähigkeit und in den Persönlichkeitseigenschaften Schadensvermeidung und Schizotypie als potenzielle Endophänotypen der Zwangsstörung. Die Ergebnisse stehen im Einklang mit dem fronto-striatalen Modell der Zwangsstörung und können als Ansatzpunkt für die Erforschung konkreter Störungsmechanismen dienen. Auf der Untersuchung von Endophänotypen basierende transdiagnostische Ansätze haben aussichtsreiche Implikationen für die zukünftige Klassifikation psychiatrischer Erkrankungen und deren Therapie.

Omnium enim rerum principia parva sunt.

Marcus Tullius Cicero, 45 v. Chr.

1 Einführung

Die Zwangsstörung ist mit einer Lebenszeitprävalenz von etwa 1–3 % (Weissman et al., 1994) eine relativ häufige psychische Erkrankung, die zu gravierenden Funktionseinbußen und Leiden bei den Betroffenen führt (Pauls, Abramovitch, Rauch, & Geller, 2014). Sie ist gekennzeichnet durch wiederkehrende intrusive Gedanken, Impulse oder Vorstellungen, die als höchst aversiv erlebt und zumeist mit repetitiven motorischen oder kognitiven Zwangshandlungen beantwortet werden (American Psychiatric Association, 2013). Der klinische Phänotyp der Zwangsstörung ist äußerst heterogen und umfasst verschiedene Symptomdimensionen, die sich in Kontrollzwänge, Waschzwänge, Ordnungs-, Symmetrie-, und Zählzwänge sowie Hort- und Sammelzwänge gliedern (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008). Das mittlere Erkrankungsalter liegt bei etwa 20 Jahren (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005), wobei 30–50 % der Patienten bereits in der Kindheit von Zwängen betroffen sind (Zohar, 1999). Obgleich Männer im Durchschnitt einen früheren Störungsbeginn aufweisen als Frauen (Geller et al., 1998), ist das Geschlechterverhältnis insgesamt ausgeglichen (Bebbington, 1998; Rasmussen & Eisen, 1990). In der Behandlung von Zwängen haben sich die kognitive Verhaltenstherapie mit Exposition und Reaktionsverhinderung sowie die Pharmakotherapie mit selektiven Serotonin-Wiederaufnahmehemmern (engl. selective serotonin reuptake inhibitors, SSRI) und dem trizyklischen Antidepressivum Clomipramin als wirksam erwiesen (Fineberg, Brown, Reghunandanan, & Pampaloni, 2012; Franklin & Foa, 2011). Unbehandelt nimmt die Erkrankung jedoch häufig einen chronischen Verlauf (Murray & Lopez, 1997; Rasmussen & Eisen, 1992; Skoog & Skoog, 1999).

Das ätiologische Modell der Zwangsstörung umfasst verschiedene biologische, psychologische und umweltbezogene Faktoren, die interaktiv zusammenwirken. Eine genetische Komponente gilt dabei als gut belegt; welche konkreten Genvarianten das Erkrankungsrisiko beeinflussen, ist jedoch weitgehend unklar (Pauls et al., 2014). Erschwert wird die Identifikation von Risikogenen insbesondere durch die hohe Komplexität und Heterogenität der Zwangsstörung. Um dieser Problematik zu begegnen, rückte der Fokus der Forschung innerhalb der letzten Jahre verstärkt auf die Untersuchung potenzieller Endophänotypen, die verglichen mit der klinischen Störung einen direkteren Bezug zu den krankheitsassoziierten Genen aufweisen sollten (Gottesman & Gould, 2003). Darüber hinaus bietet der Endophänotypenansatz

einen wichtigen Zugang zur Identifikation konkreter Störungsmechanismen (Glahn et al., 2014). In der vorliegenden Arbeit werden verschiedene aussichtsreiche Endophänotypenkandidaten anhand einer großen, vielschichtig charakterisierten Stichprobe von Zwangspatienten, deren nicht affizierten Angehörigen ersten Grades und gesunden Kontrollprobanden untersucht. Ziel ist es, kognitive und persönlichkeitsbezogene Auffälligkeiten zu identifizieren, die sowohl bei Zwangspatienten als auch bei deren Angehörigen bestehen. Der Heterogenität der Zwangsstörung wird dabei durch die Berücksichtigung von Symptomdimensionen, Komorbiditäten und weiteren klinischen Charakteristika Rechnung getragen.

Nachfolgend wird zunächst ein Überblick über die Genetik der Zwangsstörung (Kapitel 2), ihre pathophysiologischen Grundlagen (Kapitel 3) und das Endophänotypenkonzept (Kapitel 4) gegeben. Anschließend werden die neuronalen Grundlagen der Okulomotorik (Kapitel 5), welche einen methodischen Schwerpunkt dieser Dissertation darstellt, sowie die Bedeutung der Symptomdimensionen der Zwangsstörung (Kapitel 6) erläutert. In Kapitel 7 wird das Untersuchungsprogramm vorgestellt, bevor schließlich die Ergebnisse der einzelnen Originalarbeiten zusammengefasst (Kapitel 8) und diskutiert (Kapitel 9) werden.

2 Genetik der Zwangsstörung

Die Familiarität der Zwangsstörung wurde bereits in den 1930er Jahren durch erste empirische Befunde gestützt (Lewis, 1936) und seitdem durch zahlreiche weitere Untersuchungen belegt (Pauls et al., 2014). Evidenz aus Zwillings- (Iervolino, Rijsdijk, Cherkas, Fullana, & Mataix-Cols, 2011; Taylor, 2011) und Familienstudien (Grabe et al., 2006; Nestadt et al., 2000, Mataix-Cols et al., 2013) weist auf eine ausgeprägte genetische Komponente von etwa 50 % hin (van Grootheest, Cath, Beekman, & Boomsma, 2007). Die Erblichkeitsschätzungen variieren dabei zwischen 27 und 47 % bei Störungsbeginn im Erwachsenenalter und zwischen 45 und 65 % bei Beginn im Kindesalter (van Grootheest, Cath, Beekman, & Boomsma, 2005). Entsprechend sind erstgradige Angehörige von Zwangspatienten etwa fünfmal häufiger ebenfalls von Zwängen betroffen als Vergleichspersonen aus der Allgemeinbevölkerung (Grabe et al., 2006; Nestadt et al., 2000). Das Risiko an einer Zwangsstörung zu erkranken steigt zudem proportional zum Grad der genetischen Verwandtschaft an (Mataix-Cols et al., 2013). Aufbauend auf diesen formalgenetischen Studien versucht sich die Forschung mithilfe verschiedener molekulargenetischer Ansätze der Frage zu nähern, welche

spezifischen Genregionen und funktionellen Pathways dieser beobachteten Heritabilität zugrunde liegen.

2.1 Linkage-Studien

Genomweite Linkage-Studien ergaben mehrere potenziell störungsassoziierte Loci, unter anderem auf Chromosom 3q27-28 (Shugart et al., 2006) und 1p36.33-p36.32 (Mathews et al., 2012), wobei jedoch kein bis heute identifizierter Locus genomweite Signifikanz erreichte (Hanna et al., 2002; Hanna et al., 2007; Shugart et al., 2006). Linkage-Studien basieren auf dem Rational, dass Gene, die nah beieinander auf demselben Chromosom lokalisiert sind, während der Meiose nur mit geringer Wahrscheinlichkeit durch chromosomales Crossing-over voneinander getrennt und somit gekoppelt vererbt werden. Linkage-Studien erweisen sich vor allem dann als aufschlussreich, wenn eine geringe Anzahl von Genen das Erkrankungsrisiko mit jeweils großer Effektstärke beeinflusst. Zur Identifikation von Risikoallelen bei komplex vererbten Merkmalen eignen sie sich hingegen weniger gut, sodass das Ausbleiben signifikanter Zusammenhänge selbst in hinreichend großen Stichproben eine polygenetische Ätiologie der Zwangsstörung nahelegt (Pauls et al., 2014).

2.2 Kandidatengenstudien

Um den Einfluss a-priori definierter genetischer Polymorphismen auf das Zwangsstörungsrisiko zu untersuchen, wurden weiterhin zahlreiche Kandidatengenstudien durchgeführt. Basierend auf dem gegenwärtigen Verständnis der involvierten neuronalen Schaltkreise und Neurotransmittersysteme wurden vor allem Assoziationen mit serotonergen, dopaminergen und glutamatergen Genen untersucht. In einer umfassenden Metaanalyse von 20 Polymorphismen, für die jeweils Befunde aus mindestens fünf Originalarbeiten vorlagen, zeigten sich signifikante Effekte der Gene *SLC6A4* und *HTR2A*, die für den Serotonintransporter respektive den Serotonin-2A-Rezeptor kodieren (Taylor, 2013). Bei männlichen Zwangspatienten ergaben sich zudem signifikante Zusammenhänge mit *COMT* und *MAOA*, deren Genprodukte in den Abbau von Catecholaminen involviert sind. Nichtsignifikante Trends wurden für die Dopamintransporter bzw. -rezeptor kodierenden Gene *DAT1* und *DRD3* sowie für den glutamatergen Polymorphismus rs3087879 identifiziert. In einer zweiten Metaanalyse von über 200 Polymorphismen, für die jeweils weniger als fünf und vielfach

nur eine einzige Originalstudie vorlagen, sodass die Befunde mit Vorsicht zu interpretieren sind, wurden Assoziationen mit 18 weiteren Polymorphismen beobachtet (Taylor, 2013). Insgesamt stützen die Befunde aus Kandidatengenstudien die Hypothese einer polygenetischen Ätiologie der Zwangsstörung, bei der verschiedene Genregionen jeweils einen kleinen, inkrementellen Anteil zum Erkrankungsrisiko beitragen (Browne, Gair, Scharf, & Grice, 2014; Davis et al., 2013).

2.3 Genomweite Assoziationsstudien

Die beiden bisher veröffentlichten genomweiten Assoziationsstudien (GWAS) der Zwangsstörung konnten die Befunde der Kandidatengenstudien jedoch nicht replizieren und erbrachten auch darüber hinaus keine genomweit signifikanten Effekte. Die erste GWAS, welche von der International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) durchgeführt wurde, umfasste 1,465 Zwangspatienten, 5,557 abstammungsgematchte Kontrollprobanden sowie 400 Trios, die jeweils aus einem Patienten und dessen Eltern oder aus einem Patienten, einem Elternteil und einem Geschwister bestanden (Stewart et al., 2013). Die stärksten Assoziationen mit der Zwangsstörung zeigten zwei in *DLGAP1* lokalisierte Polymorphismen ($p = 2.49 \times 10^{-6}$ und $p = 3.44 \times 10^{-6}$) sowie ein SNP nahe des Gens *BTBD3* ($p = 3.84 \times 10^{-8}$ in der Trio-Analyse bzw. $p = 3.62 \times 10^{-5}$ in der Gesamtauswertung). Darüber hinaus wurde unter den Top-SNPs (mit $p < .01$) ein hochsignifikantes Enrichment von meQTLs (methylation quantitative trait loci) und eQTLs (expression quantitative trait loci) des Frontallappens beobachtet, das heißt von genetischer Variation, die mit quantitativen Veränderungen in der DNA-Methylierung respektive der Genexpression im Frontallappen assoziiert ist. Dies deutet darauf hin, dass die Top-SNPs eine Rolle in der corticalen Genexpression spielen und so möglicherweise das Risiko an einer Zwangsstörung zu erkranken vermitteln. Die zweite GWAS wurde von der OCD Collaborative Genetics Association Study Group (OCGAS) durchgeführt und umfasste 1,065 Familien inklusive 1,405 Patienten sowie 1,984 zusätzliche Kontrollprobanden (Mattheisen et al., 2015). Obgleich auch hier keine genomweit signifikanten Marker identifiziert werden konnten, zeigte sich ein signifikantes Enrichment derjenigen SNPs, die bereits in der ersten GWAS vergleichsweise geringe *p*-Werte erzielt hatten. Die stärkste Assoziation ergab sich für einen Marker nahe des *PTPRD*-Gens ($p = 4.13 \times 10^{-7}$), dessen Expressionsprodukt in

die Regulation des Zellwachstums involviert ist und zudem die Differenzierung glutamaterger Synapsen fördert.

Auch in einer kürzlich publizierten Metaanalyse der beiden GWAS, die mehr als 5,000,000 SNPs umfasste, zeigten sich keine genomweit signifikanten Zusammenhänge. Es ist anzunehmen, dass auch die gepoolte Strichprobe noch nicht groß genug war, um eine hinreichende Teststärke zur Detektion der mutmaßlich sehr kleinen Effekte einzelner Marker zu erzielen. Die hochrangigsten Haplotypenblocks waren in den Genen *CASC8/CASC11* ($p = 7.1 \times 10^{-7}$), *GRID2* ($p = 1.1 \times 10^{-6}$) und *KIT* ($p = 1.6 \times 10^{-6}$) lokalisiert (IOCDF-GC & OCGAS, 2017). Durch Aggregation zahlreicher schwach störungsassoziierter Polymorphismen in polygene Risikoscores (PRS) konnte der Case-Control-Status prädiziert werden, wobei 0.9 bzw. 0.3 % der phänotypischen Varianz in den beiden Targetstichproben durch den PRS erklärt werden konnten. Besonders hervorzuheben ist, dass 65 % der SNP-basierten Heritabilität auf SNPs mit einer Minor Allele Frequency (MAF) ≥ 40 % zurückgingen. Somit kann davon ausgegangen werden, dass das genetische Risiko für die Entwicklung einer Zwangsstörung vor allem durch häufig auftretende Polymorphismen (engl. common variants) vermittelt wird. Ferner rangiert die SNP-basierte Heritabilität der Zwangsstörung mit etwa 40 % unter den höchsten aller psychiatrischen Erkrankungen (Davis et al., 2013; IOCDF-GC & OCGAS, 2017; Sullivan et al., 2017) und liegt damit nur leicht unterhalb der Erblichkeitsschätzungen aus Familienstudien. Im Gegensatz zu anderen psychiatrischen Erkrankungen gibt es also bei der Zwangsstörung nur eine geringe „missing heritability“ (Manolio et al., 2009).

2.4 Weitere molekulargenetische Ansätze

Mit einem innovativen speziesübergreifenden Ansatz, bei dem kodierende und regulierende Elemente von 608 Genen sequenziert wurden, die sich aus Humanstudien, Maus- und Hundemodellen der Zwangsstörung ableiteten, fanden Noh et al. (2017) kürzlich Belege für eine Rolle von *HTR2A*, *NRXN1*, *CTTNBP2* und *REEP3*. Diese vier Gene zeigten in einer Stichprobe von 592 Patienten und 560 Kontrollprobanden einen starken Zusammenhang mit der Zwangsstörung und konnten zudem in einer unabhängigen größeren Stichprobe validiert werden. *NRXN1*, welches das Zelladhäsionsprotein Neurexin 1α kodiert, erreichte beim Einschluss von 33,370 populationsgematchten Kontrollprobanden sogar genomweite Signifikanz ($p = 6.37 \times 10^{-11}$). *CTTNBP2* ist mit der Erhaltung von exzitatorischen Synapsen und *REEP3* mit

dem Transport von Vesikeln assoziiert. Interessanterweise sind alle vier Gene in neuronale Pathways involviert, die bereits vorher mit der Zwangsstörung in Zusammenhang gebracht worden waren und die synaptische Konnektivität, serotonerge und glutamaterge Signalweiterleitung sowie fronto-striatale Schleifen betreffen.

Insgesamt deuten die Befunde der verschiedenen molekulargenetischen Studien darauf hin, dass Gene des glutamatergen, serotonergen und dopaminergen Systems eine Rolle in der Ätiologie der Zwangsstörung spielen. Da diese Gene innerhalb eines gemeinsamen neuronalen Netzwerkes exprimiert werden, könnten auch Interaktionen zwischen ihnen zur Erhöhung des Erkrankungsrisikos beitragen (Haber & Heilbronner, 2013; Pauls et al., 2014).

3 Pathophysiologie der Zwangsstörung: Das fronto-striatale Modell

Auf neurophysiologischer Ebene ist die Zwangsstörung insbesondere durch Dysfunktionen der cortico-striato-thalamo-corticalen (CSTC) Schleifen gekennzeichnet, welche frontale Areale wie den orbitofrontalen und den anterioren cingulären Cortex (OFC bzw. ACC), die Basalganglien und den Thalamus umfassen. Ein Ungleichgewicht zwischen dem direkten und dem indirekten Pfad innerhalb der Basalganglien führt dabei zu einer reduzierten Hemmung des Thalamus, welche über Feedbackschleifen wiederum in einer Überaktivierung des OFC und ACC resultiert (Abbildung 1). Während der direkte Pfad von den frontalen Arealen über das Striatum, den Globus pallidus internus (GPi) und die Pars reticulata der Substantia nigra (SNr) zum Thalamus führt, verläuft der indirekte Pfad vom Striatum aus zunächst über den Globus pallidus externus (GPe) und den Nucleus subthalamicus (STN) bevor er über den GPi und die SNr zum Thalamus führt. Der direkte Pfad fungiert als selbstverstärkender positiver Feedbackkreis, der zur Initiierung und Aufrechterhaltung von Verhalten beiträgt. Der indirekte Pfad stellt hingegen einen negativen Feedbackkreis dar, der eine zentrale Rolle in der Verhaltenshemmung und beim adaptiven Wechsel zwischen Verhaltensmustern spielt (Göttlich, Krämer, Kordon, Hohagen, & Zurowski, 2014; van den Heuvel et al., 2010).

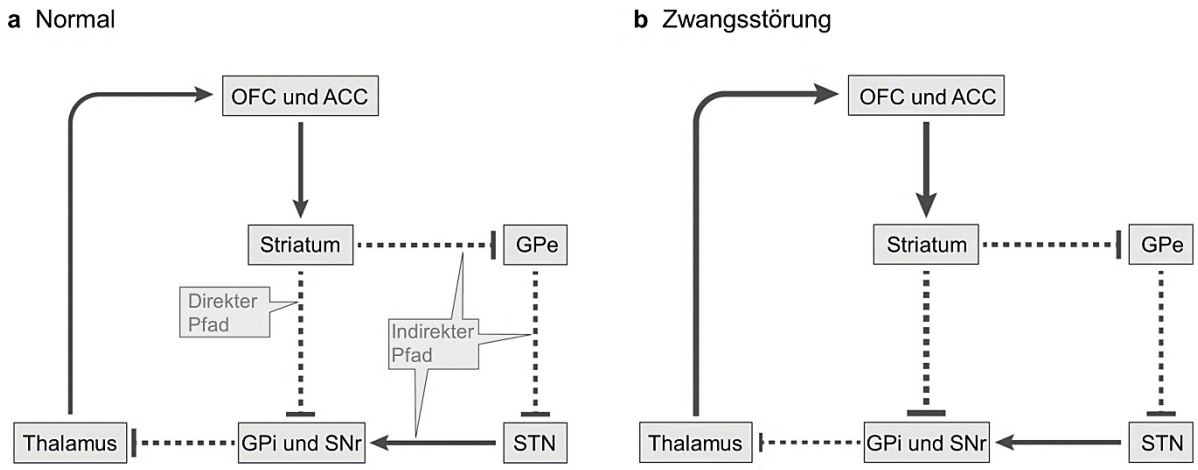

Abbildung 1. Das fronto-striatale Modell der Zwangsstörung. Die Linienstärke indiziert das Ausmaß der Aktivierung (Pfeile) bzw. Hemmung (unterbrochene Linien). Modifiziert nach Pauls et al. (2014). ACC, anteriorer cingulärer Cortex; GPe, Globus pallidus externus; GPi, Globus pallidus internus; OFC, orbitofrontaler Cortex; SNr, Substantia nigra pars reticulata; STN, Nucleus subthalamicus.

Es wird angenommen, dass die primären pathophysiologischen Veränderungen im Nucleus caudatus (CN) innerhalb des Striatums lokalisiert sind, woraus ein ineffizientes Gating auf der Ebene des Thalamus und schließlich eine Hyperaktivierung des OFC und des ACC resultieren. Auf der Verhaltensebene äußern sich diese neurophysiologischen Veränderungen in Zwangssymptomen sowie Defiziten in der exekutiven Kontrolle. Die Überaktivierung des OFC ist mit intrusiven Gedanken und die Hyperaktivität des ACC mit einer unspezifischen Angst assoziiert. Zwangshandlungen werden hingegen als Versuch verstanden, das Striatum trotz dessen Ineffizienz zu rekrutieren, um thalamisches Gating zu erzielen, sodass die Zwangsgedanken und Ängste neutralisiert werden können (Del Casale et al., 2011). Darüber hinaus spielen die CSTC Schleifen eine wichtige Rolle in der Verarbeitung von Belohnungsreizen, der Detektion von verhaltensrelevanten Stimuli und Fehlern, bei der Handlungsauswahl, Gewohnheitsbildung und motorischen Kontrolle (Arnsten et al., 2011; Fineberg et al., 2017; Lovinger, 2010; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Neuere Untersuchungen legen jedoch nahe, dass die Pathophysiologie der Zwangsstörung nicht ausschließlich auf CSTC Systeme beschränkt ist, sondern auch andere Hirnregionen wie den dorsolateralen präfrontalen Cortex (DLPFC) und den Partietallappen betrifft (Rotge et al., 2010).

3.1 Bildgebende Studien und Tiefenhirnstimulation

Das fronto-striatale Modell wird sowohl durch Befunde aus der Positronen-Emissions-Tomographie (PET) als auch aus der funktionellen Magnetresonanztomographie (fMRT) gestützt. Zwangspatienten zeigen dabei eine konsistent erhöhte Aktivierung des OFC und des bilateralen CN (Baxter et al., 1987; Menzies et al., 2008; Whiteside, Port, & Abramowitz, 2004). Ebenso weist der ACC, welcher eine zentrale Rolle in der Fehlerüberwachung und in der Bewertung von Konfliktsituationen spielt, sowohl im Ruhezustand als auch während Symptomprovokation eine Hyperaktivierung auf (Breiter et al., 1996; Swedo et al., 1989). Darüber hinaus ist die Zwangsstörung mit einer erhöhten funktionellen Konnektivität zwischen dem OFC und den Basalganglien (Beucke et al., 2013; Harrison et al., 2009) sowie einer reduzierten Konnektivität innerhalb des Default-Mode-Netzwerkes (DMN) assoziiert (Beucke et al., 2014; Peng, Xu et al., 2014).

Strukturelle MRT-Studien zeigen, dass Zwangspatienten verglichen mit gesunden Kontrollprobanden ein größeres Volumen der grauen Substanz im Striatum und im ACC sowie ein geringeres Volumen im OFC und DLPFC aufweisen (Hu et al., 2017; Piras et al., 2015; Rotge et al., 2010). Eine umfassende Metaanalyse subcorticaler Hirnregionen deutet ferner darauf hin, dass erwachsene Zwangspatienten signifikant reduzierte Hippocampus- und Pallidumvolumina aufweisen, während pädiatrische Zwangspatienten ein signifikant erhöhtes Thalamusvolumen zeigen (Boedhoe et al., 2017). Weitere Evidenz für die Involvierung der CSTC Schleifen in die Ätiologie der Zwangsstörung ergibt sich aus der Beobachtung, dass die Tiefenhirnstimulation striataler Regionen wie des Nucleus accumbens oder des ventralen CN bei etwa 60 % der vormals therapierefraktären Patienten zu einer signifikanten Verbesserung der Zwangssymptome führt (Alonso et al., 2015).

3.2 Evidenz aus Mausstudien

Genetisch veränderte Mäuse, die eine Deletion des *SAPAP3*-Gens (auch *DLGAP3* genannt) aufweisen, welches nah mit dem aus Humanstudien bekannten *DLGAP1*-Gen verwand ist und für ein postsynaptisches Gerüstprotein kodiert, zeigen eine starke Überaktivität der sogenannten Medium Spiny Neurone (MSN) im Striatum, die zu einer dysfunktionalen synaptischen Signalweiterleitung in den CSTC Schleifen beitragen und mit zwangsähnlichem Fellpflegeverhalten sowie erhöhter Ängstlichkeit einhergehen (Welch et al., 2007). Bemerkenswerterweise lassen sich diese Verhal-

tensauffälligkeiten durch die Gabe von SSRI (Welch et al., 2007) sowie durch Tiefenhirnstimulation der Capsula interna reduzieren (Pinhal et al., 2018). In ähnlicher Form führt eine chronische optogenetische Stimulation der CSTC Schleifen bei genetisch unveränderten Mäusen zu einer Überaktivität der MSN und zwanghaftem Fellpflegeverhalten (Ahmari et al., 2013). Diese Befunde legen eine potenziell kausale Rolle hyperaktiver striataler MSN in der Ätiologie der Zwangsstörung nahe.

4 Das Endophänotypenkonzept

Endophänotypen sind messbare Marker, die aufgrund geteilter genetischer Einflüsse mit einer Krankheit assoziiert sind. Es wird angenommen, dass Endophänotypen genetisch weniger komplex sind als der klinische Phänotyp und systembiologisch näher an der Ebene der Gene liegen (Gottesman & Gould, 2003; Abbildung 2). Indem sie potenziell größere genetische Effektstärken aufweisen oder die statistische Power durch das quantitative Ranking von Personen innerhalb diagnostischer Kategorien erhöhen, könnten Endophänotypen zur Identifikation von Risikogenen beitragen (Glahn et al., 2014) und zudem Aufschluss über die zugrundeliegenden Störungsmechanismen geben. In den letzten Jahren wurden spezifische, prüfbare Kriterien vorgeschlagen, um die objektive Identifikation von Endophänotypen zu erleichtern (Gottesman & Gould, 2003; Zobel & Maier, 2004). Diesen Anforderungen zufolge muss ein Endophänotyp zunächst grundsätzlich erblich (1) sowie replizierbar mit der Erkrankung assoziiert sein (2). Darüber hinaus sollte er unabhängig vom aktuellen klinischen Status und somit zeitlich stabil sein (3). Innerhalb von Familien sollte der Endophänotyp mit der Erkrankung cosegregieren (4), sodass die jeweiligen Defizite sowohl bei Patienten als auch bei deren nicht betroffenen Verwandten zu beobachten sein sollten (5). Zusätzlich ist es wichtig, dass der Endophänotyp reliabel messbar ist (6) (Waldman, 2005). Die meistuntersuchten Endophänotypenkandidaten umfassen strukturelle und funktionelle Auffälligkeiten im MRT, elektrophysiologische Parameter und kognitive Variablen. Durch die Identifikation valider Endophänotypen erhofft man sich schlussendlich nicht nur ein besseres Verständnis der Störungsätiologie, sondern auch Fortschritte in der Diagnostik, Klassifikation und Behandlung psychiatrischer Erkrankungen (Gould & Gottesman, 2006).

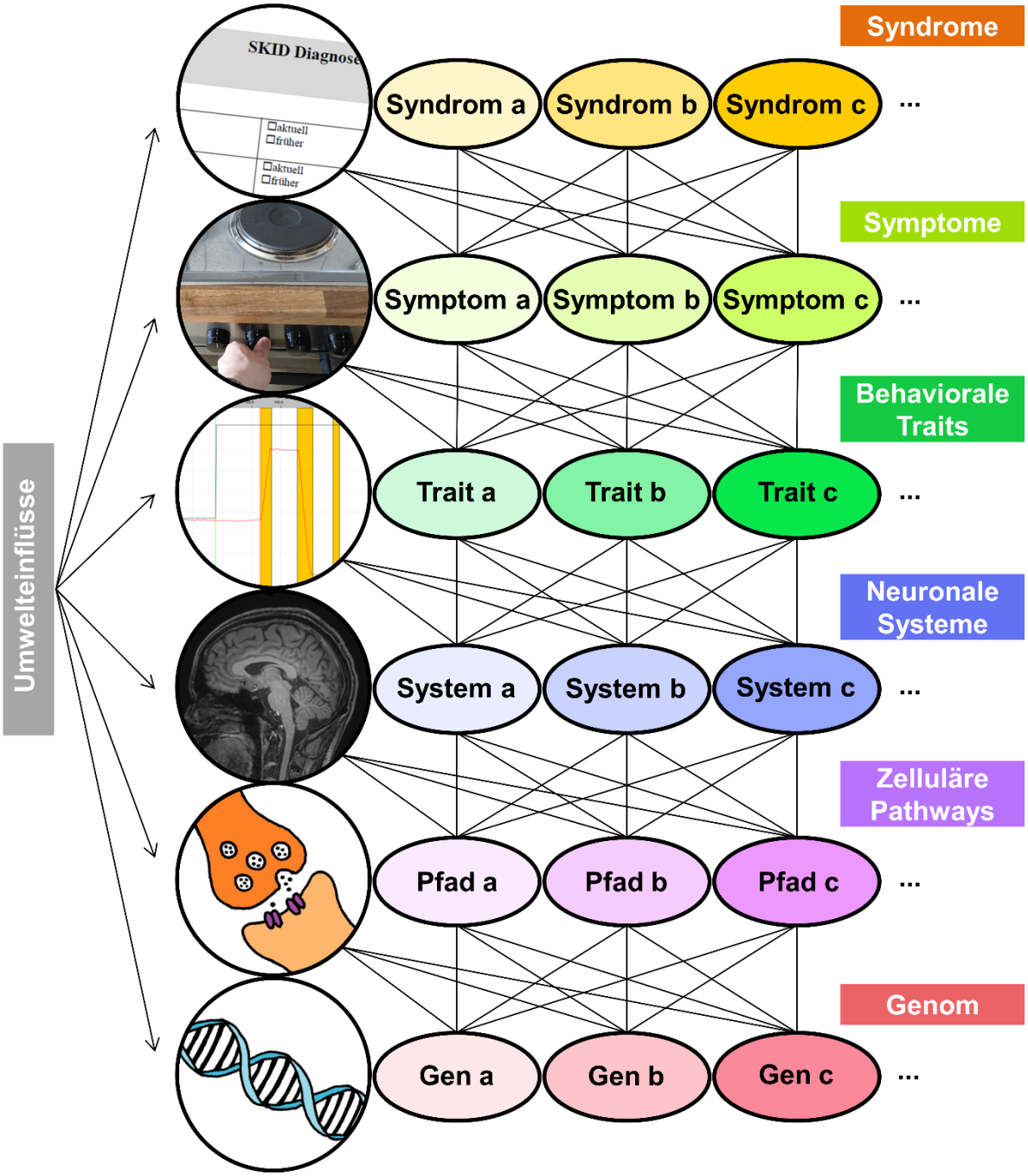

Abbildung 2. Schematische Darstellung der biologischen Pfade vom Gen zum klinischen Syndrom. Endophänotypen wie behaviorale Traits liegen näher an der Ebene der Gene als distale Krankheitsphänotypen. Modifiziert nach Siebner, Callicott, Sommer und Mattay (2009) sowie Chamberlain und Menzies (2009).

4.1 Endophänotypen der Zwangsstörung

Inzwischen liegen verschiedene Studien zu potenziellen Endophänotypen der Zwangsstörung vor, in denen Zwangspatienten und deren erstgradige Angehörige

hinsichtlich neurokognitiver, psychophysiologischer, hirnstruktureller und -funktioneller Merkmale mit Kontrollprobanden verglichen wurden. Sowohl Patienten als auch nicht betroffene Angehörige zeigen eine erhöhte Error-Related Negativity (ERN; Riesel, Endrass, Kaufmann, & Kathmann, 2011), die einen EEG-Indikator verstärkter Handlungsüberwachung darstellt und auch nach Besserung der Zwangssymptome bestehen bleibt (Riesel, Endrass, Auerbach, & Kathmann, 2015). Ein weiterer potenzieller Endophänotyp ist die Antisakkadenperformanz, bezüglich derer bei Zwangspatienten mehrfach Auffälligkeiten in Form erhöhter Antisakkadenlatenzen und/oder Fehlerraten beobachtet wurden (Damilou, Apostolakis, Thrapsanioti, Theleritis, & Smyrnis, 2016; Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992; van der Wee et al., 2006). Nicht affizierte erstgradige Angehörige von Zwangspatienten machen in der Antisakkadenaufgabe ebenfalls signifikante mehr Fehler als Kontrollprobanden (Lennertz et al., 2012). In einer Studie von Kloft, Reuter, Riesel und Kathmann (2013) wiesen Patienten und Angehörige zudem längere Latenzen bei der Ausführung volitionaler Sakkaden auf. Neuropsychologische Endophänotypenkandidaten, für die bereits Evidenz aus der Untersuchung von Patienten und Angehörigen vorliegt, umfassen die Planungsfähigkeit (Turm von London sowie Turm von Hanoi; Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Delorme et al., 2007), die kognitive Flexibilität (Wisconsin Card Sorting Test sowie Intra/Extradimensional Set Shift Task; Cavedini et al., 2010; Chamberlain et al., 2007; Rajender et al., 2011), die Inhibitionsleistung (Stopp-Signal-Aufgabe sowie Stroop Test; Chamberlain et al., 2007; Menzies et al., 2007; Rajender et al., 2011), die Entscheidungsfindung (Iowa Gambling Task; Cavedini et al., 2010; Viswanath, Reddy, Kumar, Kandavel, & Chandrashekar, 2009) sowie das nonverbale Gedächtnis (Segalas et al., 2010).

Neben geteilten kognitiven Auffälligkeiten unterscheiden sich Zwangspatienten und ihre Angehörigen auch hinsichtlich spezifischer Persönlichkeitsdimensionen signifikant von Kontrollprobanden. So weisen sowohl Patienten als auch Angehörige ersten Grades erhöhte Neurotizismus- (Samuels et al., 2000) und Schadensvermeidungswerte (Calvo et al., 2009; Ettelt et al., 2008), eine gesteigerte Prävalenz von zwanghaften Persönlichkeitsstörungen (Samuels et al., 2000) sowie eine Überschätzung von Gefahr und der eigenen Verantwortlichkeit (Rector et al., 2009) auf. Zudem zeigen Zwangspatienten und ihre Angehörigen häufiger soziale und Kommunikationsprobleme als gesunde Kontrollprobanden (Cullen et al., 2008).

Die hohe Erblichkeit der Hirnanatomie (den Barber et al., 2013; Hibar et al., 2015; van der Lee et al., 2017) und der funktionellen Resting-State-Konnektivität (Adhikari et al., 2018; Fu et al., 2015; Sinclair et al., 2015) bilden die Grundlage weiterer aussichtsreicher Endophänotypenkandidaten. Sowohl Zwangspatienten als auch deren erstgradige Angehörige weisen strukturelle Veränderungen in fronto-striatalen Netzwerken auf (Shaw et al., 2015) und zeigen verglichen mit Kontroll-probanden ähnliche Auffälligkeiten in der fraktionalen Anisotropie (FA) der weißen Substanz in einer rechten inferior-parietalen und einer rechten medial-frontalen Region (Menzies et al., 2008) sowie im linken superioren Lobulus (Peng, Shi, Shi, Miao et al., 2014). In einer weiteren Studie wiesen Patienten im Vergleich zu Kontrollprobanden eine signifikant geringere FA des linken cingulären Faserbündels auf, während Angehörige phänotypisch in der Mitte lagen (Fan et al., 2016). Ferner wurde sowohl bei Zwangspatienten als auch bei deren Angehörigen eine linksgerichtete Asymmetrie der Cortexdicke des ACC beobachtet (Peng et al., 2015). Bei der Untersuchung struktureller Netzwerkparameter zeigten sich ebenfalls übereinstimmende Auffällig-keiten bei Patienten und Angehörigen in Form einer geringeren lokalen Effizienz und reduzierten Konnektiviät innerhalb des DMN sowie einer erhöhten Interkonnektivität zwischen zwei kognitiven Netzwerken (Peng, Shi, Shi, Yang et al., 2014). Im Resting State weisen Zwangspatienten und deren nicht betroffene Angehörige zum einen eine reduzierte funktionelle Konnektivität des posterioren cingulären Cortex innerhalb des DMN auf (Peng, Xu et al., 2014). Zum anderen zeigen beide Gruppen verglichen mit Kontrollprobanden eine erhöhte funktionelle Konnektivität zwischen dem bilateralen CN und dem OFC sowie zwischen dem linken mittleren temporalen Gyrus und dem linken posterioren cingulären Cortex (Hou et al., 2014).

4.2 Hier untersuchte Endophänotypenkandidaten

In der vorliegenden Arbeit werden verschiedene Endophänotypenkandidaten hinsichtlich ihrer Auffälligkeit bei Zwangspatienten und deren erstgradigen Ange-hörigen überprüft. Einerseits werden die Persönlichkeitsmerkmale Schadensver-meidung und Schizotypie untersucht, andererseits die mittels des Turms von London erfasste Planungsfähigkeit sowie verschiedene okulomotorische Funktionen, die Antisakkaden, volitionale Sakkaden und glatte Augenfolgebewegungen umfassen.

4.2.1 Schadensvermeidung

Schadensvermeidung (engl. harm avoidance) ist eine Persönlichkeitseigenschaft, die durch exzessive Sorgen, Angst vor Ungewissheit, Schüchternheit und schnelle Ermüdbarkeit gekennzeichnet ist. Im Rahmen von Cloningers biosozialen Modell der Persönlichkeit (Cloninger et al., 1987) wird sie als automatische Tendenz, intensiv auf aversive Stimuli zu reagieren, beschrieben. Die Neigung zu Schadensvermeidung weist eine hohe Heritabilität von 42–57 % auf (Garcia et al., 2013; Gillespie, Cloninger, Heath, & Martin, 2003; Keller, Coventry, Heath, & Martin, 2005) und ist über die Lebenspanne stabil (Josefsson et al., 2013). Verglichen mit gesunden Kontrollprobanden zeigen Zwangspatienten erhöhte Schadensvermeidungswerte (Ettelt et al., 2008; Kim, Kang, & Kim, 2009; Richter, Summerfeldt, Joffe, & Swinson, 1996), die nach Symptomreduktion weitgehend bestehen bleiben (Lyoo, Yoon, Kang, & Kwon, 2003). Zudem liegt erste Evidenz vor, dass sich auch nicht betroffene Angehörige von Zwangspatienten durch eine erhöhte Schadensvermeidungsneigung auszeichnen (Ettelt et al., 2008; Calvo et al., 2009). Die Persönlichkeitseigenschaft Schadensvermeidung stellt somit einen relevanten Endophänotypenkandidat dar, der das familiäre Zwangsstörungsrisiko teilweise mediieren könnte (Ettelt et al., 2008). Die Ausprägung der Schadensvermeidungsneigung wird mittels des Temperament and Character Inventory (TCI; Cloninger, Svrakic, & Przybeck, 1993; Richter, Eisemann, & Richter, 2000) erhoben, welches die Subskalen „antizipatorische Sorgen und Pessimismus vs. ungehemmter Optimismus“, „Angst vor dem Ungewissen“, „Schüchternheit gegenüber Fremden“ und „Ermüdbarkeit und Schwäche vs. Vitalität“ umfasst.

4.2.2 Schizotypie

Schizotypie beschreibt eine Konstellation subklinischer schizophrenie- und psychoseartiger Persönlichkeitsmerkmale, die sich durch Eigentümlichkeiten im Verhalten, im Denken und bei der Wahrnehmung auszeichnet (Lenzenweger, 2010; Vollema & van den Bosch, 1995). Analog zur klinischen Schizophrenie umfasst die Schizotypie positive, negative und desorganisierte Dimensionen (Raine, 2006). Hochschizotypische Personen sind sehr sensibel und messen vielen Ereignissen, Dingen und Personen in ihrer Umgebung eine besondere emotionale Bedeutung bei. Aufseiten der Negativsymptomatik stehen reduzierte emotionale, physische und soziale Funktionen, sodass Interaktionen mit anderen Menschen als unangenehm

empfunden und eher gemieden werden. Die desorganisierte Dimension der Schizotypie ist durch Gedankenstörungen und bizarres Verhalten gekennzeichnet (Ettinger et al., 2015). Obgleich nur ein geringer Anteil hochschizotypischer Personen klinisch erkrankt, stellt die Schizotypie einen Risikofaktor für die Entstehung einer Schizophrenie oder einer Störung aus dem Schizophreniespektrum dar (Gooding, Tallent, & Matts, 2005). Im Rahmen von Familienstudien wurden bei erstgradigen Angehörigen von Schizophreniepatienten erhöhte Schizotypiewerte beobachtet (Calkins, Curtis, & Grove, 2004; Kendler, McGuire, Gruenberg, & Walsh 1995), woraus auf eine signifikante genetische Überlappung von Schizophrenie und Schizotypie geschlossen wird (siehe Review von Barrantes-Vidal, Grant, & Kwapil, 2015). Die Erblichkeit der Schizotypie beträgt etwa 30–50 % (Ericson et al., 2011; Lin et al., 2007; Linney et al., 2003; Kendler & Hewitt, 1992). Zwangspatienten weisen verglichen mit gesunden Kontrollprobanden signifikant erhöhte Schizotypiewerte auf (Rossi & Daneluzzo, 2002). Eine hochschizotypische Persönlichkeit scheint dabei insbesondere mit einer erhöhten Rate von Ordnungs-, Symmetrie- und Kontrollzwängen, aggressiven Zwangsgedanken, allgemeiner Psychopathologie und der globalen Zwangssymptomschwere assoziiert zu sein (Brakoulias et al., 2014; Sobin et al., 2000; Yamamoto et al., 2012). Inwiefern auch erstgradige Angehörige von Zwangspatienten eine erhöhte Schizotypie aufweisen, wurde bis jetzt noch nicht untersucht. Vor dem Hintergrund der hohen genetischen Überlappung zwischen der Schizophrenie und der Zwangsstörung (Brainstorm Consortium et al., 2018) ist jedoch zu vermuten, dass Endophänotypen der Schizophrenie auch aussichtsreiche Kandidaten für die Zwangsstörung sein könnten.

4.2.3 Turm von London

Der Turm von London (TvL) ist ein neuropsychologischer Test zur Erfassung der Planungsfähigkeit. Dabei müssen verschiedenfarbige Kugeln auf unterschiedlich langen Stäben umgesteckt werden, um sie mit möglichst wenigen Zügen von einer Startposition in eine Zielposition zu überführen. Die Probanden werden instruiert, ihre Züge gedanklich zu planen, bevor sie mit der eigentlichen Ausführung beginnen. Die Anforderung des Planungsprozesses besteht darin, dass die mentale Repräsentation einer gegebenen Situation durch die Generierung verschiedener hypothetischer Lösungsschritte in einen angestrebten Zielzustand transformiert werden muss (Kaller, Unterrainer, & Stahl, 2012). Die erfolgreiche Lösung eines TvL-Problems ist somit

abhängig von der Fähigkeit, eine passende Handlungssequenz auszuwählen und diese umzusetzen. Drei Metaanalysen (Abramovitch, Abramowitz, & Mittelman, 2013; Shin, Lee, Kim, & Kwon, 2014; Snyder, Kaiser, Warren, & Heller, 2014) sowie ein qualitatives Review (Abramovitch & Cooperman, 2015) zeigen, dass Zwangspatienten signifikante Defizite in der mittels des TvL erfassten Planungsfähigkeit aufweisen, die zudem mit einer reduzierten Rekrutierung fronto-striataler Hirnregionen einhergehen (van den Heuvel et al., 2005). Die Evidenz für ähnliche Defizite bei erstgradigen Angehörigen ist jedoch inkonsistent. Während Delorme et al. (2007) berichten, dass Angehörige von Zwangspatienten verglichen mit Kontrollprobanden aus der Allgemeinbevölkerung eine verminderte Lösungsgenauigkeit und erhöhte Bearbeitungszeiten im TvL aufweisen, fanden Viswanath et al. (2009) keine derartigen Defizite. Zhang et al. (2015) beobachteten bei Zwangspatienten und deren Angehöringen verlängerte Reaktionszeiten hinsichtlich TvL-Problemen mit höherem Schwierigkeitsgrad, bezüglich einfacher Probleme allerdings nicht. In zwei weiteren Studien zeigte sich eine reduzierte Planungsfähigkeit bei Zwangspatienten, nicht jedoch bei deren Angehörigen (Lennertz et al., 2012; Rajender et al., 2011). Hingegen wiesen in einer fMRT-Version des TvL sowohl Zwangspatienten als auch deren erstgradige Angehörige eine Hypoaktivierung des DLPFC sowie eine reduzierte fronto-striatale Konnektivität während des Planens auf (Vaghi et al., 2017). Die inkonsistente Befundlage scheint einerseits durch die relativ geringen Stichprobengrößen bedingt zu sein; andererseits könnten Unterschiede in den jeweils verwendeten TvL-Paradigmen die Inkonsistenzen erklären.

In den meisten Studien wird die Schwierigkeit eines TvL-Problems lediglich anhand der Anzahl der zur Lösung minimal notwendigen Züge definiert, obgleich zahlreiche weitere Problemparameter wie die Zielhierarchie (engl. goal hierarchy) und die Suchtiefe (engl. search depth) die Schwierigkeit beeinflussen (Kaller, Unterrainer, Rahm, & Halsband, 2004; Kaller, Rahm, Köstering, & Unterrainer, 2011). Die Suchtiefe eines TvL-Problems ist definiert als die Anzahl von Zwischenzügen, die erforderlich ist, bevor die erste Kugel auf ihrer Zielposition platziert werden kann. Die Zielhierarchie hingegen beschreibt die Eindeutigkeit, mit der sich die Sequenz der Züge aus der Zielposition herleiten lässt. Wenn alle Kugeln übereinander auf demselben Stab angeordnet sind (voller Turm), ist die Zielhierarchie eindeutig. Wenn zwei oder mehr Kugeln auf demselben Stab stecken, während mindestens eine Kugel auf einem anderen Stab steckt (partieller Turm), ist die Zielhierarchie teilweise ambigue und

wenn alle Kugeln auf unterschiedlichen Stäben angeordnet sind (flache Position), spricht man von einer ambiguen Zielhierarchie (Kaller et al., 2011; Abbildung 3).

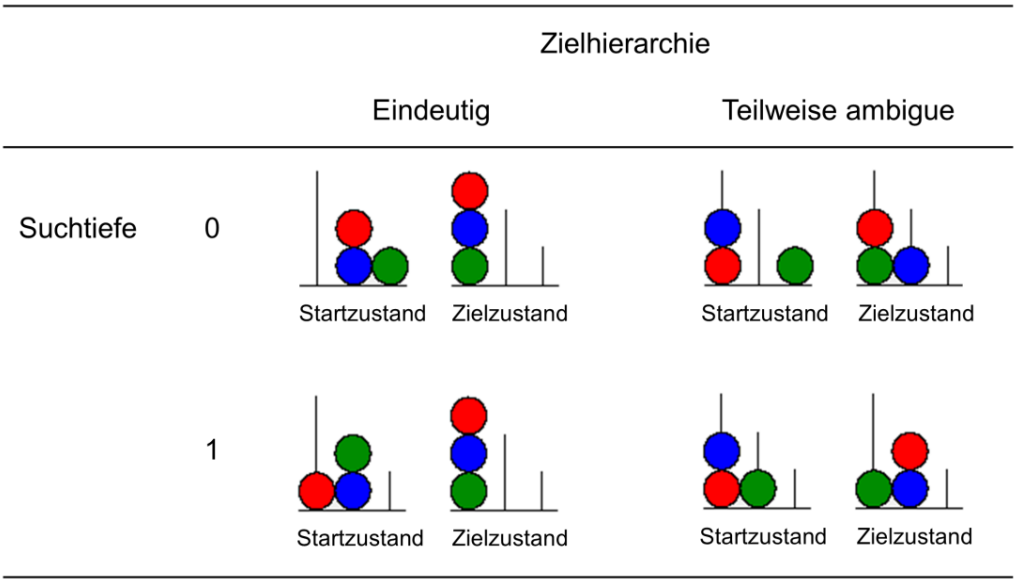

Abbildung 3. Turm von London (TvL). Dargestellt sind vier TvL-Probleme, die jeweils mit einer optimalen Anzahl von vier Zügen zu lösen sind, sich jedoch hinsichtlich der Problemparameter Suchtiefe (0 vs. 1) und Zielhierarchie (eindeutig vs. teilweise ambigue) unterscheiden.

Eine unzureichende Berücksichtigung dieser Problemparameter kann zur Task Impurity, Unterspezifikation kognitiver Prozesse und damit einhergehenden Problemen der Reliabilität und Konstruktvalidität beitragen (Berg, Byrd, McNamara, & Case, 2010; Köstering et al., 2015). Hingegen könnte die systematische Variation von Problemparametern differenzielle Planungsdefizite in klinischen Stichproben aufzeigen. So weisen Parkinsonpatienten beispielsweise Performanzdefizite bei TvL-Problemen mit ambiguer Zielhierarchie auf, zeigen jedoch keine suchtiefebezogenen Auffälligkeiten in der Planung (McKinlay et al., 2008).

4.2.4 Sakkaden

Die Sakkade ist eine schnelle ballistische Augenbewegung hin zu einem neuen Fixationspunkt (Liversedge, Gilchrist, & Everling, 2011). Sie kann entweder reflexiv, zum Beispiel durch einen peripher erscheinenden Zielreiz, initiiert oder willentlich in eine spezifische Richtung ausgeführt werden. Im Rahmen der Prosakkadenaufgabe wird der Proband instruiert, auf einen Fixationsreiz in der Mitte des Computerbildschirms zu blicken und, sobald ein Zielreiz auf der rechten oder linken Bildschirmseite

erscheint, so schnell und genau wie möglich eine Sakkade zu diesem Zielreiz auszuführen (Abbildung 4a). Die Reizpräsentation bei der Antisakkadenaufgabe ist identisch, jedoch besteht die Instruktion nun darin, bei Erscheinen des peripheren Reizes möglichst schnell und akkurat eine Sakkade in die entgegengesetzte Richtung auszuführen (Abbildung 4b). Die Antisakkadenaufgabe stellt insofern erhöhte Anforderungen an kognitive Kontrollfunktionen, als dass das neuronale Signal zur Ausführung einer Antisakkade das präpotente Prosakkadensignal übertreffen muss (Cutsuridis, 2017). Im Rahmen der volitionalen Sakkadenaufgabe blickt der Proband ebenfalls zunächst auf einen Fixationsreiz, jedoch erscheint zu keiner Zeit ein äußerer Zielreiz. Die Richtung, in die eine Sakkade ausgeführt werden soll, wird durch eine Veränderung des zentralen Fixationsreizes indiziert (Kloft, Kischkel, Kathmann, & Reuter, 2011; Abbildung 4c). Somit bedarf die volitionale Sakkade zwar einer willentlichen Initiierung und Lenkung, im Gegensatz zur Antisakkade muss jedoch kein konkurrierendes Prosakkadensignal übertroffen werden.

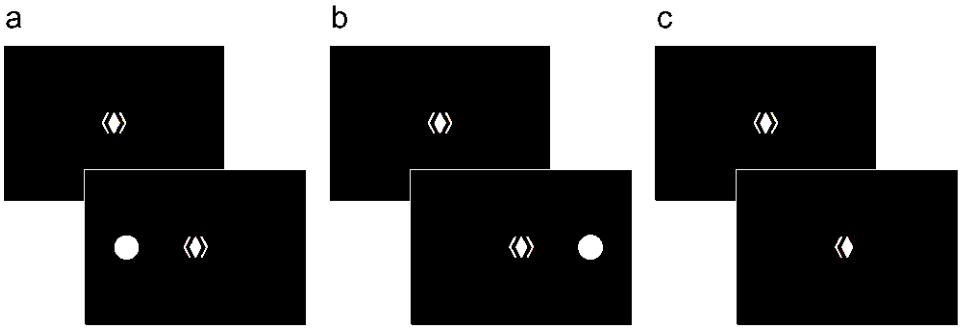

Abbildung 4. Stimulusanordnung in drei verschiedenen Sakkadenparadigmen. *a.* Prosakkadenaufgabe. *b.* Antisakkadenaufgabe. *c.* Volitionale Sakkadenaufgabe. Die zu Beginn eines Trials präsentierten Fixationsreize sind über die drei Aufgaben hinweg identisch. In jedem dargestellten Trial soll eine Sakkade nach links ausgeführt werden. Zur besseren Sichtbarkeit sind die Stimuli in Relation zur Bildschirmgröße überproportional groß dargestellt.

Die Befundlage hinsichtlich okulomotorischer Auffälligkeiten bei Zwangspatienten ist weitgehend inkonsistent (Jaafari et al., 2011). Während in einigen Studien erhöhte Fehlerraten und/oder längere Latenzen in der Antisakkadenaufgabe beobachtet wurden (Damilou et al., 2016; Lennerzt et al., 2012; Maruff, Purcell, Tyler, Pantelis, & Currie, 1999; McDowell & Clementz, 1997; Tien et al., 1992; van der Wee et al., 2006), fanden andere Autoren keine signifikanten Unterschiede zwischen Zwangspatienten und gesunden Kontrollprobanden (Kloft et al., 2011; Spengler et al.,

2006). Erste Evidenz weist jedoch darauf hin, dass auch nicht affizierte Angehörige von Zwangspatienten eine erhöhte Fehlerrate in der Antisakkadenaufgabe zeigen, sodass diese Auffälligkeit einen potenziellen Endophänotyp der Zwangsstörung darstellen könnte (Lennertz et al., 2012). Ferner wurden sowohl bei Zwangspatienten als auch bei deren erstgradigen Angehörigen verlängerte volitionale Sakkadenlatenzen beobachtet (Kloft et al., 2011; 2013). Die studienübergreifend inkonsistenten Ergebnisse scheinen zum einen auf die Verwendung unterschiedlicher Okulomotorikparadigmen zurückzuführen zu sein. Zum anderen ist, insbesondere vor dem Hintergrund der heterogenen Symptomatik der Zwangsstörung, anzunehmen, dass variierende Stichprobencharakteristika zu Inkonsistenzen in der Befundlage beigetragen haben. Darüber hinaus ist die Teststärke der meisten bis jetzt publizierten Studien durch eine zu geringe Stichprobengröße eingeschränkt.

4.2.5 Glatte Augenfolgebewegungen

Glatte Augenfolgebewegungen (engl. smooth pursuit eye movements, SPEM) ermöglichen die Verfolgung eines sich bewegenden Objektes allein mit den Augen, indem die Bewegungsgeschwindigkeit der Augen der Geschwindigkeit des Zielreizes möglichst genau angepasst wird (Leigh & Zee, 2015). SPEM funktionieren dabei über sensomotorische Feedbackmechanismen, denen ein weites okulomotorisches Netzwerk zugrunde liegt. Um die SPEM-Performanz zu erfassen, werden häufig Zielreize verwendet, die sich mit sinusförmiger Geschwindigkeit gleichsam eines schwingenden Pendels in horizontaler Ebene von links nach rechts und wieder zurück bewegen. Der Beitrag prädiktiver Mechanismen lässt sich untersuchen, indem der Zielreiz während der SPEM-Ausführung für ein kurzes Zeitintervall ausgeblendet wird. Jede residuale Augenbewegung, die nach einer Latenz von 300 ms fortbesteht, basiert auf der Prädiktion des SPEM-Systems (Becker & Fuchs, 1985; Lencer & Trillenberg, 2008). Verglichen mit einer kontinuierlichen Präsentation führt das Ausblenden des Zielreizes zur verstärkten Rekrutierung der Basalganglien und zusätzlicher präfrontaler Ressourcen (Lencer, Nagel, et al., 2004; Nagel, Sprenger, Hohagen, Binkofski, & Lencer, 2008). Ferner scheinen prädiktive SPEM eine erhöhte Anforderung an das Arbeitsgedächtnis zu stellen (Ding, Powell, & Jiang, 2009; Moates et al., 2012; siehe jedoch Kattoulas et al., 2011).

Auch hinsichtlich SPEM zeigen sich bei Zwangspatienten keine konsistenten Defizite (Jaafari et al., 2011; McCarthy, 2011). Zwar weisen Patienten mit

Zwangsstörung in einigen Studien eine reduzierte Ratio zwischen Augen- und Zielreizgeschwindigkeit (sog. Gain) auf (Gambini, Abbruzzese, & Scarone, 1993; Lencer, Trillenberg, et al., 2004; Sweeney, Palumbo, Shear, & Halper, 1992), jedoch konnte dieser Befund in anderen Untersuchungen nicht repliziert werden (Damilou et al., 2016; Farber, Clementz, & Swerdlow, 1997; Spengler et al., 2006). Studien zu prädiktiven SPEM bei Zwangspatienten liegen bis jetzt nicht vor. Ebenso gibt es noch keine SPEM-Untersuchungen an erstgradigen Angehörigen von Zwangspatienten.

5 Neuronale Grundlagen der Okulomotorik

Da es sich bei der okulomotorischen Schleife um eine der parallelen fronto-striatalen Schleifen handelt (Alexander et al., 1990), welche dem CSTC Modell der Zwangsstörung zugrunde liegen, bietet die Analyse von Augenbewegungen einen aufschlussreichen Zugang zur Untersuchung der fronto-striatalen Integrität (Lencer, Nagel et al., 2004). Insbesondere die in die Ausführung von Sakkaden und SPEM involvierten Hirnregionen weisen prägnante Überlappungen mit den bei Zwangspatienten strukturell und funktionell auffälligen Arealen auf.

5.1 Sakkadische Augenbewegungen

Durch konvergente Befunde aus Läsions-, Bildgebungs- und neurophysiologischen Tierstudien sind die neuronalen Grundlagen sakkadischer Augenbewegungen gut beschrieben. Das Sakkadennetzwerk umfassen sowohl corticale Hirnregionen als auch die Basalganglien, den Thalamus, den superioren Colliculus, die Formatio reticularis im Hirnstamm sowie das Cerebellum (Abbildung 5; Munoz & Everling, 2004). Visuelle Information gelangt über den retinotektalen Pfad zu den superfiziellen Schichten des superioren Colliculus (SCs) sowie über den retino-geniculo-corticalen Pfad zum primären visuellen Cortex und wird von zahlreichen extrastriatalen visuellen Arealen verarbeitet, bevor sie motorische Regionen erreicht (Maunsell & Newsome, 1987). Das laterale intraparietale Areal (LIP) im posterioren parietalen Cortex stellt eine wichtige Schnittstelle zwischen sensorischer und motorischer Verarbeitung dar (Andersen, 1997). Es projiziert sowohl zu den intermediären Schichten des superioren Colliculus (SCi; Paré & Wurtz, 2001) als auch zu frontalen Arealen, einschließlich des frontalen Augenfelds (FEF), des supplementären Augenfelds (SEF) und des DLPFC (Schall, 1997). Während das FEF eine

wichtige Rolle in der willentlichen Ausführung von Sakkaden spielt (Dias & Segraves, 1999), ist das SEF in die internal gesteuerte Entscheidungsfindung und die Sequenzierung von Sakkaden involviert (Coe, Tomihara, Matsuzawa, & Hikosaka, 2002; Stuphorn, Taylor, & Schall, 2000). Der DLPFC ist mit exekutiven Funktionen, räumlichem Arbeitsgedächtnis und der Inhibition automatischer, reflexiver Reaktionen assoziiert (Guitton, Buchtel, & Douglas, 1985), sodass ihm insbesondere bei der Antisakkadenaufgabe eine wesentliche Relevanz beigemessen wird (Hutton, 2008). Die frontalen Regionen projizieren schließlich zum SCi, der einen zentralen Knotenpunkt im prämotorischen Schaltkreis darstellt, in dem corticale und subcorticale Signale integriert werden (Munoz & Fecteau, 2002). Entgegen früherer Annahmen scheint die behavioral hemmende Funktion des DLPFC auf neuronaler Ebene allerdings durch einen exzitatorischen Einfluss auf den SC gekennzeichnet zu sein (Johnston et al., 2013). FEF, SEF und SC projizieren direkt zur paramedianen Formatio reticularis, um eine Sakkade zu initiieren oder zu unterdrücken. Darüber hinaus projizieren frontale okulomotorische Areale auch zum CN, der seinerseits über den direkten sowie über den indirekten Pfad zur SNr projiziert. Die SNr hemmt nicht nur den Thalamus innerhalb der CSTC Schleifen, sondern ebenfalls den SCi und beeinflusst somit die Sakkadeninitiation. Dysfunktionale Aktivierungsmuster innerhalb der CSTC Schleifen, wie sie bei Zwangspatienten beobachtet werden, könnten folglich zu einer Disinhibition des SCi beitragen, welche in Defiziten bei der Antisakkaden-aufgabe resultieren könnte.

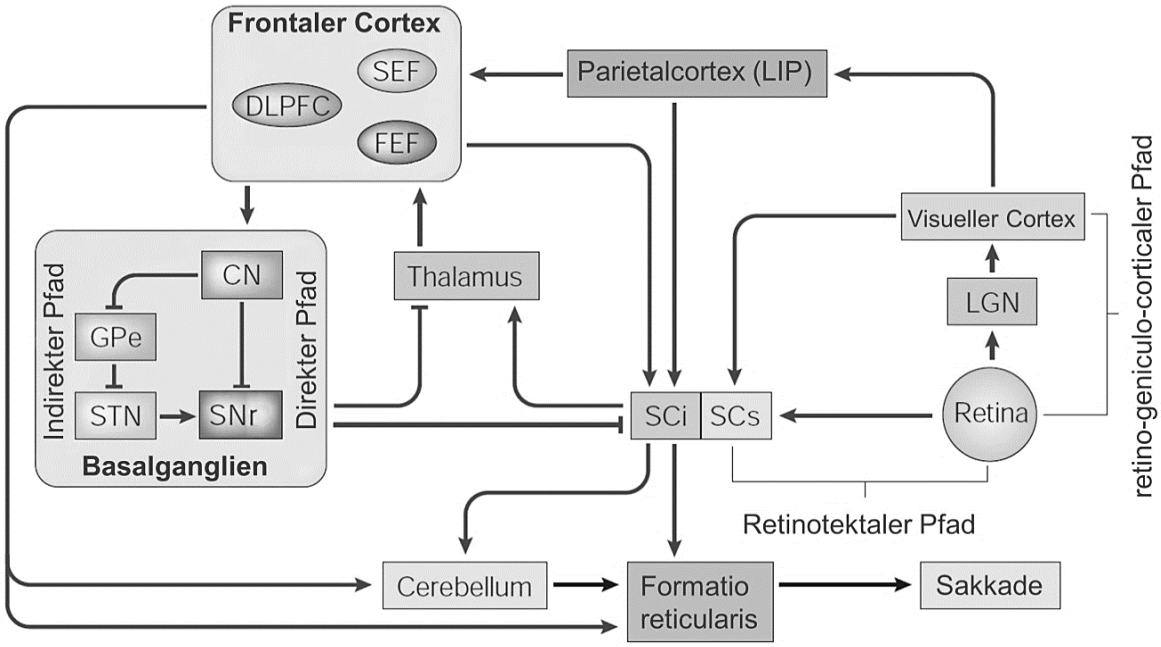

Abbildung 5. Neuronaler Schaltkreis sakkadischer Augenbewegungen. Modifiziert nach Munoz und Everling (2004). CN, Nucleus caudatus; DLPFC, dorsolateraler präfrontaler Cortex; FEF, frontales Augenfeld; GPe, Globus pallidus externus; LGN, Corpus geniculatum laterale; LIP, laterale intraparietale Areal; SCi, intermediären Schichten des superioren Colliculus; SCs, superfizielle Schichten des superioren Colliculus; SEF, supplementäres Augenfeld; SNr, Substantia nigra pars reticulata; STN, Nucleus subthalamicus.

In Abhängigkeit der Latenz zwischen Stimuluspräsentation und Sakkadenausführung lassen sich Expresssakkaden und reguläre Sakkaden unterscheiden. Während Expresssakkaden Latenzen von 80 bis 130 ms umfassen, sind reguläre Sakkaden langsamer als 130 ms, wobei die Schwellenwerte über verschiedene Studien hinweg leicht variieren (Fischer & Ramsperger, 1984; Smyrnis, 2008). Fehlern in der Antisakkadenaufgabe, die mit Expresssakkadenlatenz oder mit regulärer Latenz erfolgen, liegen differentielle neuronale Mechanismen zugrunde (Coe & Munoz, 2017). Bevor in einem Antisakkaden-Trial der periphere Reiz erscheint, muss eine präemptive Hemmung der sakkadengenerierenden Neurone im SCi bestehen, um zu verhindern, dass durch die automatische visuelle Reaktionstendenz zum Reiz hin ein Expressfehler ausgelöst wird. Potenzieller Ursprung dieser präemptiven Hemmung sind Fixationsneurone innerhalb des SCi, die während der visuellen Fixation tonisch aktiv sind und bei der Sakkadenausführung aufhören zu feuern (Munoz & Wurtz, 1992). Zudem weisen auch frontale Areale sowie die Basalganglien eine vor Stimuluspräsentation bestehende Aktivierung auf, die im Sinne einer top-down

gesteuerten Hemmung maßgeblich zur Inhibition des SCi beizutragen scheint (Coe & Munoz, 2017). Nach Erscheinen des peripheren Reizes müssen volitionale Antisakkadensignale mit automatischen, visuell initiierten Prosakkadensignalen konkurrieren und diese schließlich übertreffen, um einen Fehler mit regulärer Latenz zu verhindern. Patienten mit verschiedenen neurologischen und psychiatrischen Erkrankungen, die den Frontallappen oder die Basalganglien betreffen, weisen unterschiedliche Auffälligkeiten hinsichtlich der beiden Fehlerarten auf. Während bei Parkinsonpatienten beispielsweise mehr Fehler mit längeren Latenzen zu beobachten sind (Cameron et al., 2012), zeigen Patienten mit amyotropher Lateralsklerose mehr Expressfehler (Witiuk et al., 2014); Patienten mit Aufmerksamkeitsdefizit-Hyperaktivitätsstörung machen sowohl mehr Fehler mit regulären als auch mit Expresslatenzen (Hakvoort Schwerdtfeger et al., 2013). Die differenzierte Betrachtung der unterschiedlichen Fehlerarten in der Antisakkadenaufgabe kann somit Aufschlüsse über störungsspezifische Defizite in der inhibitorischen Kontrolle geben (Coe & Munoz, 2017).

5.2 Glatte Augenfolgebewegungen

Hirnphysiologisch sind SPEM mit Regionen assoziiert, die sowohl in die Bewegungsverarbeitung als auch in die Prädiktion involviert sind und primär das FEF, das SEF, das parietale Augenfeld (PEF) sowie das bewegungssensitive Areal V5 umfassen (Lencer & Trillenberg, 2008). Ferner scheinen auch die Basalganglien mit der Ausführung von SPEM assoziiert zu sein (Lencer, Nagel et al., 2004). Nachdem die Signale des retinalen Abbilds den visuellen Cortex erreicht haben, werden sie zum extrastriatalen visuellen Areal V5 weitergeleitet, welches wiederum zum medialen superioren temporalen visuellen Areal projiziert. Von dort aus werden die Signale zu frontalen Hirnregionen gesendet. Diese umfassen sowohl das FEF, wo der okulomotorische Befehl zu SPEM generiert wird, als auch andere frontale Areale wie das SEF und den DLPFC, die zusammen mit dem PEF in Reaktionsselektions- und Monitoringprozesse involviert sind. Extrastriatale und frontale visuelle Areale projizieren zu den pontinen Nuclei, die sowohl Augenbewegungen als auch das visuelle Informationssignal enkodieren. Von dort aus wird die Information über das Cerebellum zu den vestibulären Nuclei und schließlich zu den okulomotorischen Nuclei weitergeleitet. Zwischen Cerebellum und corticalen Arealen bestehen enge reziproke Verbindungen (Lencer & Trillenberg, 2008). Prädiktive SPEM, die sich durch

kurzzeitiges Ausblenden des Zielreizes untersuchen lassen, sind im Vergleich zu kontinuierlichen SPEM mit einer stärkeren Rekrutierung der Basalganglien und zusätzlicher präfrontaler Ressourcen assoziiert (Lencer, Nagel, et al., 2004; Nagel et al., 2008).

6 Symptomdimensionen der Zwangsstörungen

Der klinische Phänotyp der Zwangsstörung ist durch eine starke Heterogenität gekennzeichnet, die so weit geht, dass zwei Patienten, die beide die Diagnosekriterien der Zwangsstörung erfüllen, mitunter gänzlich verschiedene Symptommuster aufweisen. Durch faktorenanalytische Auswertung der Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Symptomcheckliste (Goodman et al., 1989), die einen umfangreichen Katalog von Zwangsgedanken und -handlungen darstellt, lassen sich konsistent vier bis sechs übergeordnete Symptomdimensionen identifizieren. Eine Metaanalyse von 21 faktorenanalytischen Studien zeigte, dass eine Vierfaktorenlösung die Struktur der klinischen Symptome am besten widergibt (Bloch et al., 2008). Der erste Faktor repräsentiert dabei Ordnungs-, Symmetrie-, Zähl- und Wiederholungszwänge, während der zweite Faktor tabuisierte Gedanken zu den Themenbereichen Aggressivität, Sexualität und Religiosität sowie somatische Zwangsgedanken und Kontrollzwänge einschließt. Der dritte Faktor umfasst Waschzwänge und Kontaminationsängste, der vierte Sammelzwänge. Die verschiedenen Symptomdimensionen sind mit differenziellen Auffälligkeiten in kognitiven Funktionen (Leopold & Backenstrass, 2015), hirnstrukturellen Parametern (Alvarenga et al., 2008; Koch et al., 2012; Lázaro et al., 2014; van den Heuvel et al., 2009) sowie hirnphysiologischen Reaktionen auf Symptomprovokation (Mataix-Cols et al., 2004; Murayama et al., 2013) assoziiert. Basierend auf diesen Befunden schlugen Nakao, Okada und Kanba (2014) eine Überarbeitung des fronto-striatalen Modells der Zwangsstörung vor, das symptomspezifische Schleifen umfasst. Kontrollzwänge werden darin mit Dysfunktionen im ACC und im Striatum assoziiert, während große corticale Hirnregionen inklusive des DLPFC, des ventrolateralen präfrontalen Cortex und des temporalen Cortex sowie auch das Cerebellum mit Waschzwängen in Verbindung gebracht werden (Nakao et al., 2014).

Auf kognitiver Ebene zeigen Patienten mit Kontrollzwängen im Vergleich zu Patienten mit prädominantem Waschzwang signifikant größere Defizite in einer Vielzahl von neuropsychologischen Tests, insbesondere in den Domänen

Planungsfähigkeit/Problemlösen und Reaktionsinhibition (Leopold & Backenstrass, 2015). Diese Beobachtung legt nahe, dass die inkonsistente Befundlage hinsichtlich exekutiver Funktionseinschränkungen bei Zwangspatienten teilweise durch die Heterogenität des klinischen Phänotyps zu erklären sein könnte. Konkret könnten Unterschiede in der Stichprobenzusammensetzung bezüglich der Ausprägung einzelner Zwangsdimensionen dazu beigetragen haben, dass in einigen Studien kognitive Defizite gefunden wurden, in anderen jedoch nicht. Darüber hinaus zeichnen sich die distinkten Symptomdimensionen durch Unterschiede in Komorbiditätsmustern (Baer, 1994; Hasler et al., 2005; Torres et al., 2016), Heritabilitäten (Katerberg et al., 2010; Leckman et al., 2003) und Zusammenhängen mit genetischen Polymorphismen (Cavallini, Di Bella, Siliprandi, Malchiodi, & Bellodi, 2002; Hasler, Kazuba, & Murphy, 2006; Melo-Felippe et al., 2016) aus, was darauf hinweist, dass unterschiedliche Suszeptibilitätsgene zur Ausprägung der einzelnen Subdimensionen des Zwangs beitragen könnten. In einer Zwillingsstudie von Iervolino et al. (2011) zeigte sich, dass die phänotypische Heterogenität der Zwangsstörung am besten durch ein multivariates Modell erklärt wird, das sowohl gemeinsame als auch dimensionsspezifische genetische und umweltbezogenen Faktoren umfasst. Ein Modell mit einem einzigen dimensionsübergreifenden latenten Faktor wurde hingegen klar zurückgewiesen (Iervolino et al., 2011). Insgesamt deuten diese Befunde darauf hin, dass den unterschiedlichen Symptomdimensionen der Zwangsstörung zumindest teilweise spezifische ätiologische Faktoren zugrunde liegen. Entsprechend stellt ihre Berücksichtigung einen wichtigen Aspekt in der Untersuchung von potenziellen Endophänotypen der Zwangsstörung dar.

Während frühere Studien oftmals kategoriale Gruppen wie Waschzwangs- und Kontrollzwangspatienten miteinander verglichen haben, bietet ein dimensionaler Ansatz mehrere Vorteile. Einerseits spiegelt er die klinische Realität wider, da der Großteil der Zwangspatienten nicht nur Symptome in einem spezifischen Bereich aufweist, sondern in mehreren (Mataix-Cols et al., 2005). Andererseits geht die Konzipierung kontinuierlicher Dimensionen mit einer größeren Varianz und somit einer höheren Teststärke einher. Die Untersuchung der Symptomdimensionen erfolgte in der vorliegenden Arbeit sowohl anhand des Obsessive Compulsive Inventory-Revised (OCI-R; Foa et al., 2002; Gönner, Leonhart, & Ecker, 2002) als auch durch die faktorenanalytische Auswertung der Y-BOCS Symptomcheckliste. Entsprechend des etablierten Vorgehens von Baer et al. (1994) wurden die 13 Oberkategorien der

Y-BOCS Symptomcheckliste bei Vorliegen bzw. Fehlen von mindestens einem Symptom aus der entsprechenden Kategorie mit 1 bzw. 0 kodiert. Anschließend wurden diese binären Variablen in eine explorative Faktorenanalyse mit Varimax-Rotation eingepflegt und im Sinne des Kaiser-Guttman-Kriteriums alle resultierenden Faktoren mit einem Eigenwert > 1 extrahiert. Da zwanghaftes Horten im DSM-5 inzwischen eine eigene Störungskategorie innerhalb des Zwangsspektrums darstellt, wurde diese Erkrankung neben der Erfassung mittels der genannten Fragebögen auch als komorbide Diagnose dokumentiert.

7 Die EPOC-Studie

Sämtliche Daten wurden im Rahmen des durch die Deutsche Forschungsgemeinschaft (DFG) geförderten Projektes „Neurokognitive Endophänotypen der Zwangsstörung und deren Hirnkorrelate“ (engl. Endophenotypes of Obessive-Compulsive Disorder, EPOC) erhoben. Ziel dieser bizentrischen Studie, die an der Humboldt-Universität zu Berlin und der Rheinischen Friedrich-Wilhelms-Universität Bonn unter der Leitung von Herrn Prof. Dr. rer. nat. Dipl.-Psych. Norbert Kathmann und Herrn Prof. Dr. phil. Dipl.-Psych. Michael Wagner durchgeführt wurde, ist die Erforschung potenzieller Endophänotypen der Zwangsstörung und deren genetischer Grundlage. Zu diesem Zweck wurden Patienten mit Zwangsstörung und deren nicht betroffene erstgradige Angehörige sowie gesunde Kontrollprobanden aus der Allgemeinbevölkerung untersucht. Die umfangreiche Datenerhebung umfasste klinische Interviews, Fragebögen, neuropsychologische und okulomotorische Testungen sowie Blutproben zur Analyse genetischer und epigenetischer Einflüsse. Am Berliner Standort wurden darüber hinaus auch Elektroenzephalogramme (EEG) und MRT-Daten erhoben.

7.1 Die EPOC-Stichprobe

Insgesamt wurden $n = 205$ Patienten mit Zwangsstörung, $n = 110$ nicht betroffene erstgradige Angehörige von Zwangspatienten ($n = 76$ Eltern, $n = 25$ Geschwister und $n = 9$ Kinder) sowie $n = 213$ gesunde Kontrollprobanden aus der Allgemeinbevölkerung in die Studie eingeschlossen, wobei die Stichprobengröße über die verschiedenen Paradigmen hinweg variiert. Die Zusammensetzung der Stichprobe ist in Tabelle 1 dargestellt.

Tabelle 1

Zusammensetzung der Gesamtstichprobe im EPOC-Projekt

		Zentrum		
		Berlin	Bonn	Gesamt
Gruppe	Zwangspatienten	135	70	205
	Angehörige	61	49	110
	Kontrollprobanden	149	64	213
Gesamt		345	183	528

Der Anteil männlicher Probanden beträgt bei den Zwangspatienten 44.4 %, bei den erstgradigen Angehörigen 32.7 % und bei den Kontrollprobanden 39.2 %. Über die drei Gruppen hinweg unterscheidet sich das Geschlechterverhältnis nicht signifikant ($\chi^2(2) = 4.49$, $p = .11$). Die Zwangspatienten sind im Mittel 33.14 ($SD = 10.68$) und die Kontrollprobanden 34.52 ($SD = 12.58$) Jahre alt. Mit einem mittleren Alter von 47.27 ($SD = 13.80$) Jahren sind die Angehörigen signifikant älter als die beiden anderen Gruppen ($F(2,525) = 53.83$, $p < .001$). Dem wird bei der Analyse von Variablen, die signifikant mit dem Probandenalter korrelieren, wie beispielsweise der Antisakkadenlatenz, durch Berücksichtigung des Alters als Kovariate Rechnung getragen. Ein Großteil der Zwangspatienten hat eine zusätzliche komorbide Erkrankung (am häufigsten eine Depression: $n = 48$ aktuelle Episode, $n = 75$ remittiert) und ist mit SSRI oder anderen Antidepressia mediziert ($n = 94$ innerhalb der letzten vier Wochen, $n = 29$ früher). Weitere Stichprobencharakteristika sind in Tabelle 2 dargestellt.

Tabelle 2

Demographische und klinische Charakteristika der EPOC-Gesamtstichprobe

	Zwangspatienten	Angehörige	Kontrollen	Statistik	*p*-Wert
N	205	110	213		
Geschlecht (m:w)	91:114	36:74	80:133	$\chi^2(2) = 4.49$	.11
Alter	33.14 (10.68)	47.27 (13.80)	34.52 (12.58)	$F(2,525) = 53.83$	< .001
OCI-R	27.78 (12.17)	6.81 (6.61)	4.58 (4.58)	$F(2,521) = 420.13$	< .001
BDI-II	18.80 (10.62)	5.89 (6.80)	3.07 (4.20)	$F(2,521) = 229.23$	< .001
MADRS	11.98 (8.87)	-	-		
Y-BOCS	22.31 (6.58)	-	-		
Störungsbeginn	21.60 (11.03)	-	-		

Anmerkung: BDI-II, Beck Depressions-Inventar-II; MADRS, Montgomery-Asberg Depression Rating Scale; OCI-R, Obsessive-Compulsive Inventory-Revised; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

7.2 Studienprozedur und Untersuchungsprogramm

Die Rekrutierung der Zwangspatienten und deren erstgradiger Angehöriger erfolgte über die Hochschulambulanz der Humboldt-Universität zu Berlin sowie über die Spezialambulanz für Zwangsstörungen des Universitätsklinikums Bonn. Der Angehörigenstatus wurde darüber validiert, dass der zugehörige Indexpatient entweder selbst in die Studie eingeschlossen wurde, er den Testleitern aus dem klinischen Versorgungskontext bekannt war oder ein ärztliches Dokument vorlag, das die Zwangserkrankung des Indexpatienten bestätigte. Kontrollprobanden wurden über Aushänge und Aufrufe in lokalen Printmedien rekrutiert. Generelle Einschlusskriterien waren:

- Alter zwischen 18 und 65 Jahren
- normale oder zur Normalität korrigierte Sehfähigkeit
- verbaler IQ > 80
- fließendende Deutschsprachigkeit
- Einwilligungsfähigkeit

Die allgemeinen Ausschlusskriterien umfassten:

- Lebenszeitdiagnose von Substanzabhängigkeit, bipolarer Störung oder Störungen aus dem Schizophreniespektrum
- neurologische Erkrankungen des zentralen Nervensystems
- andere mit den Untersuchungen interferierende Erkrankungen oder Behinderungen
- Einnahme von Benzodiazepinen innerhalb der letzten Woche sowie von Neuroleptika innerhalb der letzten drei Monate

Darüber hinaus wurden erstgradige Angehörige und gesunde Kontroll-probanden nicht in die Studie eingeschlossen, wenn eine Lebenszeitdiagnose für eine Zwangs- oder Ticstörung, das Tourette-Syndrom oder eine aktuelle schwerwiegende Achse-I-Störung vorlag. Ferner durfte bei Kontrollprobanden keine positive Familien-anamnese für eine Zwangsstörung bei erstgradigen Verwandten sowie keine mehr als einwöchige Einnahme psychotroper Medikamente in den letzten drei Monaten

vorliegen. Nach telefonischem Screening hinsichtlich dieser Ein- und Ausschlusskriterien wurden die Probanden zur Studienteilnahme eingeladen, die am Bonner Standort zumeist ein bis zwei und in Berlin aufgrund zusätzlicher bildgebender sowie neurophysiologischer Testungen etwa drei Untersuchungstage umfasste.

Zu Beginn wurden die Probanden ausführlich über die Studieninhalte, ihre persönlichen Rechte und mögliche Risiken der Teilnahme informiert. Alle Probanden gaben ihr schriftliches Einverständnis. Die Studie entsprach den Vorgaben der Deklaration von Helsinki und war von den zuständigen Ethikkommissionen in Bonn und Berlin genehmigt.

Ein typischer Untersuchungstag am Bonner Standort begann mit einer Blutabnahme, bei der, möglichst im nüchternen Zustand, 20 ml Blut (zwei 7.5 ml EDTA-Röhrchen und zwei 2.5 ml PAXGENE-Röhrchen) für genetische und epigenetische Analysen abgenommen wurden. Eine geringe Anzahl von Probanden (< 10 %), die Bedenken gegenüber der Blutabnahme äußerte, gab alternativ eine Speichelprobe ab. Anschließend erfolgte ein ausführliches diagnostisches Interview, welches das Strukturierte Klinische Interview für DSM-IV (SKID-I; First, Spitzer, Gibbon, & Williams, 1997; Wittchen, Zaudig, & Fydrich, 1997), das Family History Screen (FHS; Weissman et al., 2000) sowie Fragen bezüglich Geburtskomplikationen und des sozioökonomischen Status umfasste. Bei Zwangspatienten wurden zusätzlich die Y-BOCS (Goodman et al., 1989; Hand & Büttner-Westphal, 1991), die Yale Globale Tic-Schweregrad-Skala (YGTSS; Leckman et al., 1989; Steinhausen, 2002) und die Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979; Neumann & Schulte, 1989) durchgeführt. Vor oder während des Interviews hatten die Teilnehmer Gelegenheit, nach Belieben ein kleines Frühstück einzunehmen. Im Anschluss an das Interview folgten die okulomotorische und behaviorale Testung. Zu den Okulomotorikparadigmen zählten glatte Augenfolgebewegungen, volitionale Sakkaden, klassische Pro- und Antisakkaden sowie affektive Pro- und Antisakkaden. Ferner wurden die simple Reaktionszeit (engl. simple reaction time) und die Auswahlreaktionszeit (engl. choice reaction time) erfasst. Ein Teil der Probanden führte zudem die Stopp-Signal-Aufgabe durch, bevor diese in späteren Erhebungen aufgrund mangelnder Evidenz für Gruppenunterschiede durch einen TvL-Task und eine räumliche Arbeitsgedächtnisaufgabe ersetzt wurde, welche beide an einem Tablet bearbeitet wurden. Zum Schluss der Untersuchung füllten die Probanden

elektronisch ein Fragebogenset in deutscher Sprache aus, das folgende Skalen umfasste:

- Basisfragebogen (Demographie, Medikation, Psychotherapie, Body Mass Index etc.)
- Edinburgh Handedness Scale (Oldfield, 1971)
- Adult ADHD Self-Report Scale v1.1 (ASRS; Kessler et al., 2005)
- Beck Depressions-Inventar-II (BDI-II; Steer, Ball, Ranieri, & Beck, 1997; Hautzinger, Keller, & Kühner, 2006)
- Fragebogen zu Exekutiven Funktionen (Barkley, Murphy, & Fischer, 2008)
- Life Experience Survey (LES; Sarason et al., 1978)
- Urbanität des Lebensraums in den ersten 15 Lebensjahren (Mortensen, 1999)
- Fagerström-Test für Nikotinabhängigkeit (FTNA; Bleich, Havemann-Reinecke, & Kornhuber, 2002; Fagerström, 1978)
- Obsessive-Compulsive Trait Core Dimensions Questionnaire (OC-TCDQ; Ecker, Gönner, & Wilm, 2011; Summerfeld, Kloosterman, Parker, Antony, & Swinson, 2001)
- Obsessive-Compulsive Inventory-Revised (OCI-R; Foa et al., 2002; Gönner et al., 2002)
- Fragebogen zu Persönlichkeitsstörungen des Strukturierten Klinischen Interviews (SKID-II; First et al., 1995; Wittchen et al., 1997)
- State-Trait Anxiety Inventory (STAI; Laux & Spielberger, 2001; Spielberger, Gorsuch, & Lushene, 1970)
- Neurotizismus und Extraversion mittels NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992)
- Schadensvermeidung mittels Temperament and Character Inventory (TCI; Cloninger et al., 1993; Richter et al., 2000)
- Childhood Trauma Questionnaire (CTQ; Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Wingenfeld et al., 2010)
- Y-BOCS Symptomcheckliste (nur bei Zwangspatienten; Goodman et al., 1989)
- Wortschatztest (WST; Schmidt & Metzler, 1992)

Am Berliner Standort wurden an weiteren Testungstagen EEG- und MRT-Daten erhoben. Die EEG-Erhebung schloss ein Resting-State-EEG, einen passiven Beobachtungs-Task (engl. passive viewing task) sowie die Eriksen-Flanker-Aufgabe mit ein. Die MRT-Untersuchung umfasste T1-, T2- und Diffusions-Tensor-Bildgebung (DTI), ein funktionelles Resting-State-MRT und die Messung der Hirnaktivität während der Eriksen-Flanker-Aufgabe. Im Rahmen jedes Testungsteils (Okulomotorik und behaviorale Testung, EEG, MRT) wurden die State-Ängstlichkeit mittels STAI X1 (Laux & Spielberger, 2001; Spielberger et al., 1970) sowie bei Patienten die akute Belastung durch Zwangsgedanken und -handlungen erfasst.

7.3 Aufzeichnung der Augenbewegungen

Zur Aufzeichnung von Augenbewegungen können verschiedene Methoden genutzt werden. Während in früheren Studien vornehmlich die Elektrookulographie (EOG) verwendet wurde, sind heute zumeist videobasierte Methoden das Mittel der Wahl, die auf der kombinierten Erfassung der Pupille und der cornealen Reflexion einer Infrarot-Lichtquelle beruhen – so auch in der EPOC-Studie, in der am Berliner Standort der EyeLink II und in Bonn der EyeLink 2000 (beide SR Research, Mississauga, Ontario, Kanada) genutzt wurden. Die gleichzeitige Messung der Pupille und der cornealen Reflexion erlaubt dabei eine Differenzierung von Kopf- und Augenbewegungen. Während sich bei einer Augenrotation die relative Position vom Pupillenzentrum zur cornealer Reflexion ändert, bleibt sie bei kleineren Kopfbewegungen weitgehend konstant (Duchowski, 2007). Unter Berücksichtigung der im Rahmen der Kalibrierungsprozedur erhobenen exemplarischen Datenpunkte kann basierend auf der gemessenen Distanz zwischen den Zentren der Pupille und der Cornea-Reflexion kontinuierlich die Blickposition geschätzt werden.

Die während der verschiedenen Okulomotorikparadigmen aufgezeichneten Rohdaten umfassen die räumlichen x- und y-Koordinaten der Blickposition des rechten Auges im zeitlichen Verlauf. Im Rahmen der Datenverarbeitung, die in der vorliegenden Arbeit mithilfe des SR Research Data Viewers (Version 1.11.900; SR Research, Mississauga, Ontario, Kanada) erfolgte, wurden in den Rohdaten Fixationen, Sakkaden und Blinzler anhand spezifischer Positions-, Geschwindigkeits- und Beschleunigungskriterien identifiziert. In weiteren Analyseschritten wurden unter Berücksichtigung von Aufgaben- und Trialcharakteristika wie dem Präsentationszeitpunkt und der Richtung des Zielreizes die jeweils relevanten Sakkaden ausgewählt

und ihre Charakteristika extrahiert. Die verwendeten Messwerte sind in Tabelle 3 zusammengefasst.

Tabelle 3

Überblick über die verwendeten Messwerte in den SPEM- und Sakkadenaufgaben

			Berechnung	
Task	Variable	Definition	auf Trial-Ebene	auf Ebene eines Probanden
SPEM	Gain (%)	Verhältnis zwischen Augen- und Zielreizgeschwindigkeit innerhalb eines vordefinierten Zeitfensters	(Augengeschwindigkeit / Zielreizgeschwindigkeit) × 100	Mittelwert über alle Zeitfenster mit hinreichender Qualität
Pro-, Anti- und volitionale Sakkaden	Richtungsfehler (%)	Die erste Sakkade nach Zielreizerscheinen wird in die falsche Richtung ausgeführt	Fehler ja/nein	(Anzahl der Fehler / (Anzahl der korrekten Reaktionen + Anzahl der Fehler)) × 100
	Latenz (ms)	Zeitintervall zwischen Erscheinen des peripheren Reizes (Pro- und Antisakkaden) bzw. des richtungsweisenden zentralen Reizes (volitionale Sakkaden) und des Sakkadenbeginns	Zeitpunkt Sakkadenbeginn - Zeitpunkt Zielreizerscheinen	a) Mittelwert über alle Trials mit korrekter Reaktion b) Streuung über alle Trials mit korrekter Reaktion
	Amplitude (°)	Absolute Differenz zwischen horizontaler Start- und Zielposition der Sakkade (oft auch in Relation zur Zielreizamplitude gesetzt, insb. wenn diese nicht konstant ist)	| x-Koordinate Sakkadenzielposition - x-Koordinate Sakkadenstartpunkt |	Mittelwert über alle Trials mit korrekter Reaktion

8 Kurzzusammenfassungen der einzelnen Publikationen

Im Folgenden sind die fünf Publikationen, die dieser kumulativen Dissertation zugrunde liegen, in Form von Kurzzusammenfassungen dargestellt. Die Originalstudien sind der Arbeit angehängt. Folgende Veröffentlichungen bilden die Grundlage dieser Dissertation:

- Bey, K., Lennertz, L., Riesel, A., Klawohn, J., Kaufmann, C., Heinzel, S., Grützmann, R., Kathmann, N., & Wagner, N. (2017). Harm avoidance and childhood adversities in patients with obsessive-compulsive disorder and their unaffected first-degree relatives. *Acta Psychiatrica Scandinavica*, *135(4),* 328–338.

- Bey, K.*, Kloft, L.*, Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Meyhöfer, I., Kathmann, N., & Wagner, M. (2017). Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives. *Psychophysiology, 54*(9), 1284–1294.
- Bey, K.*, Meyhöfer, I.*, Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Ettinger, U., Kathmann, N., & Wagner, M. (2018). Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience*.
- Bey, K.*, Kaufmann, C.*, Lennertz, L., Riesel, A., Klawohn, J., Heinzel, S., Grützmann, R., Kathmann, N., & Wagner, M. (2018). Impaired planning in patients with obsessive-compulsive disorder and unaffected first-degree relatives: Evidence for a cognitive endophenotype. *Journal of Anxiety Disorders*, *57*, 24–30.
- Bey, K., Lennertz, L., Grützmann, R., Heinzel, S., Kaufmann, C., Klawohn, J., Riesel, A., Meyhöfer, I., Ettinger, U., Kathmann, N., & Wagner, M. (2018). Impaired antisaccades in obsessive-compulsive disorder: Evidence from meta-analysis and a large empirical study. *Frontiers in Psychiatry*, *9*, 284.

8.1 Harm avoidance and childhood adversities in patients with obsessive-compulsive disorder and their unaffected first-degree relatives

Zwangspatienten zeigen verglichen mit gesunden Kontrollprobanden eine erhöhte Ausprägung der Persönlichkeitseigenschaft Schadensvermeidung (Ettelt et al., 2008; Kim et al., 2009; Richter et al., 1996), die durch exzessive Sorgen, Angst vor Ungewissheit, Schüchternheit sowie schneller Ermüdbarkeit gekennzeichnet ist und auch nach Symptomreduktion weitgehend bestehen bleibt (Lyoo et al., 2003). Zudem liegt erste Evidenz vor, dass sich nicht betroffene Angehörige ersten Grades von Zwangspatienten ebenfalls durch eine erhöhte Schadensvermeidungsneigung auszeichnen (Ettelt et al., 2008; Calvo et al., 2009). Diese Persönlichkeitseigenschaft stellt somit einen potenziellen Endophänotyp der Zwangsstörung dar, der das familiäre Erkrankungsrisiko teilweise mediieren könnte (Ettelt et al., 2008). Traumatische Lebensereignisse in der Kindheit spielen ebenfalls eine wichtige Rolle in der Ätiologie der Zwangsstörung. So berichten Zwangspatienten insbesondere mehr emotionalen Missbrauch und emotionale Vernachlässigung in der Kindheit als gesunde Kontroll-

probanden (Lochner et al., 2002). Kindheitliche Traumata scheinen dabei das Risiko für die Entstehung einer Zwangsstörung in Interaktion mit genetischen Prädispositionen zu beeinflussen (Hemmings et al., 2013; McGregor et al., 2016).

Anhand einer Stichprobe von $n = 169$ Zwangspatienten, $n = 57$ nicht betroffenen erstgradigen Angehörigen von Zwangspatienten und $n = 157$ gesunden Kontrollprobanden wurde in der vorliegenden Studie untersucht, wie Schadensvermeidung und kindheitliche Traumata zur Ätiologie der Zwangsstörung beitragen können. Basierend auf der Annahme eines Diathese-Stress-Modells wurde erwartet, dass sowohl Patienten als auch erstgradige Angehörige erhöhte Schadensvermeidungswerte zeigen sollten, die eine zugrundeliegende Vulnerabilität repräsentieren, während vermehrte traumatische Kindheitserlebnisse nur bei Zwangspatienten zu beobachten sein sollten. Schadensvermeidung wurde mittels des Temperament and Character Inventory (TCI; Cloninger et al., 1993; Richter et al., 2000) und traumatische Kindheitserlebnisse mittels des Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997; Wingenfeld et al., 2010) erfasst.

Sowohl Patienten als auch Angehörige zeigten verglichen mit gesunden Kontrollprobanden signifikant erhöhte Schadensvermeidungswerte. Zudem wiesen Zwangspatienten signifikant höhere Werte auf als Angehörige. Dieses Muster zeigte sich in allen Subskalen der Schadensvermeidung und blieb auch nach Berücksichtigung der depressiven und zwangsbezogenen Symptomschwere bestehen. Ferner korrelierte die Ausprägung der Schadensvermeidung signifikant positiv mit den Symptomdimensionen Zwangsgedanken/Kontrollzwänge und Waschzwänge/Kontamination. Hinsichtlich traumatischer Kindheitserlebnisse berichteten Zwangspatienten signifikant höhere Werte als Kontrollprobanden, Angehörige jedoch nicht. Während die CTQ-Gesamtskala nicht mit spezifischen Zwangssymptomdimensionen assoziiert war, ergaben sich für die drei Missbrauchssubskalen, das heißt emotionaler, physischer und sexueller Missbrauch, signifikante Zusammenhänge mit dem Faktor Zwangsgedanken/Kontrollzwänge.

Insgesamt stärken diese Befunde die Rolle einer erhöhten Schadensvermeidungsneigung als Endophänotyp der Zwangsstörung und stützen die Annahme eines Diathese-Stress-Modells. Während sowohl Zwangspatienten als auch ihre Angehörigen erhöhte Schadensvermeidungswerte aufwiesen, welche mutmaßlich eine zugrundeliegende Vulnerabilität widerspiegeln, wurden vermehrte traumatische Kindheitserlebnisse, insbesondere emotionaler Missbrauch, emotionale Vernach-

lässigung und Inkonsistenzerleben, nur bei Patienten beobachtet. Die Ergebnisse stehen im Einklang mit der Annahme, dass eine Prädisposition zu erhöhten Angstreaktionen gegenüber unbekannten oder stressvollen Situationen und Reizen in Abhängigkeit von protektiven oder aversiven Umwelteinflüssen unterschiedliche Entwicklungen nehmen kann. Frühe aversive Erlebnisse können die Aktivität der Hypothalamus-Hypophysen-Nebennierenrinden-Achse (HPA-Achse) nachhaltig bis ins Erwachsenenalter hinein beeinflussen, was zur Entstehung psychiatrischer Erkrankungen beitragen kann (Faravelli et al., 2012). Weiterhin weist empirische Evidenz darauf hin, dass die Assoziation zwischen kindheitlichem Missbrauch und psychischer Belastung durch maladaptive Persönlichkeitseigenschaften mediiert wird (Spinhoven, Elzinga, Van Hemert, de Rooij, & Penninx, 2016). Nachfolgende Studien sollten untersuchen, inwiefern sich die hier beobachteten Befunde im Längsschnitt replizieren lassen und welche mediierenden biologischen Mechanismen dabei wirksam sind.

8.2 Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives

Die Zwangsstörung ist sowohl hinsichtlich ihres klinischen Phänotyps als auch auf neuropsychologischer Ebene durch Defizite in der zielgerichteten Handlungskontrolle gekennzeichnet (Gillan et al., 2011; Gillan & Robbins, 2014). Ein etabliertes Paradigma, um diese endogene Handlungsinitiierung zu untersuchen, ist die volitionale Sakkadenaufgabe. Volitionale Sakkaden werden im Gegensatz zu reflexiven Prosakkaden nicht durch das Erscheinen eines peripheren Reizes getrieben, sondern bedürfen einer willentlichen Initiierung, die durch eine arbiträre Veränderung des zentralen Fixationsreizes instruiert wird. Sowohl Zwangspatienten als auch ihre erstgradigen Angehörigen zeigten in einer präliminären Studie erhöhte Latenzen bei der Ausführung volitionaler Sakkaden, weshalb diese Auffälligkeit als potenzieller Endophänotyp der Zwangsstörung diskutiert wurde (Kloft et al., 2013).

Die vorliegende Studie strebte an, diese Befunde in einer größeren unabhängigen Stichprobe zu replizieren. Einhundertfünfzehn Zwangspatienten, 103 gesunde Kontrollprobanden sowie 31 nicht affizierte Angehörige ersten Grades von Zwangspatienten führten eine Prosakkaden- und eine volitionale Sakkadenaufgabe durch, während ihre Augenbewegungen von einem Eyetracker aufgezeichnet wurden. Neben der Latenz der Sakkaden wurden auch deren intrapersonelle Streuung sowie

deren Amplitude analysiert. Zusätzlich wurden Lateralitätsasymmetrien zwischen rechts- und linksgerichteten Sakkaden exploriert.

Erwartungskonform waren die Latenzen in der volitionalen Sakkadenaufgabe über alle drei Gruppen hinweg signifikant länger als in der Prosakkadenaufgabe. Im Unterschied zu früheren Studien wiesen jedoch weder Zwangspatienten noch deren Angehörige Defizite in der Ausführung volitionaler Sakkaden auf. Medizierte und unmedizierte Patienten unterschieden sich nicht signifikant voneinander und auch das Vorliegen einer depressiven Komorbidität hatte keinen Einfluss auf die Performanz. Ferner zeigten sich keine signifikanten Zusammenhänge zwischen der volitionalen Sakkadenleistung und einzelnen Symptomdimensionen der Zwangsstörung. Während hinsichtlich der Sakkadenlatenzen und deren intrapersoneller Variabilität keine Lateralitätseffekte beobachtet wurden, wiesen rechtsgerichtete Sakkaden über alle Gruppen hinweg eine signifikant größere Amplitude auf als linksgerichtete.

Zusammenfassend ist festzuhalten, dass die Performanz in einer volitionalen Sakkadenaufgabe keinen aussichtreichen Endophänotyp der Zwangsstörung darzustellen scheint. Die ausbleibende Replikation kann dabei nicht durch eine unzureichende Teststärke erklärt werden, da die aktuelle Stichprobe etwa fünfmal so viele Patienten und Kontrollprobanden umfasst wie die Vorarbeit von Kloft et al. (2013). Der gruppenübergreifende Effekt einer rechtsseitigen Asymmetrie der Sakkadenamplituden ist konsistent mit Befunden aus der Allgemeinbevölkerung (Vergilino-Perez et al., 2012), bedarf jedoch weiterer validierender Forschung.

8.3 Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder

Die bei Zwangspatienten beobachteten Dysfunktionen in den CSTC Schleifen implizieren korrespondierende okulomotorische Defizite. Empirische Evidenz für Auffälligkeiten in SPEM ist jedoch inkonsistent. Während einige Studien eine reduzierte Ratio zwischen Augen- und Zielreizgeschwindigkeit (sog. Gain) bei Zwangspatienten beobachteten, fanden andere keine Defizite in SPEM (Jaafari et al., 2011; McCarthy, 2011). Schizotypische Persönlichkeitseigenschaften könnten in diesem Kontext eine relevante Variable darstellen, da sie sowohl mit der Zwangsstörung als auch mit Auffälligkeiten in SPEM assoziiert sind. Inwiefern potenzielle Defizite in SPEM und erhöhte Schizotypiewerte das genetisch vermittelte Risiko für

eine Zwangsstörung mediieren und entsprechend auch in erstgradigen Angehörigen von Zwangspatienten zu beobachten sind, wurde bis jetzt noch nicht erforscht.

Vor diesem Hintergrund wurde in der vorliegenden Studie anhand einer Strichprobe von $n = 168$ Zwangspatienten, $n = 93$ nicht betroffenen erstgradigen Angehörigen von Zwangspatienten und $n = 171$ gesunden Kontrollprobanden untersucht, ob erhöhte Schizotypiewerte und SPEM-Defizite aussichtsreiche Endophänotypenkandidaten der Zwangsstörung darstellen. Die Probanden führten eine SPEM-Aufgabe durch, die nicht nur klassische kontinuierliche, sondern auch prädiktive SPEM erfasste, bei denen die Basalganglien sowie präfrontal Areale in stärkerem Maße involviert sind (Lencer, Nagel, et al., 2004; Nagel et al., 2008).

Die Ergebnisse zeigen, dass sich Zwangspatienten und Angehörige sowohl hinsichtlich der klassischen als auch hinsichtlich der prädiktiven SPEM nicht signifikant von gesunden Kontrollprobanden unterscheiden. In Bezug auf die Schizotypie wiesen Zwangspatienten und erstgradige Angehörige jedoch signifikant erhöhte Werte auf. Bei unmedizierten und depressionsfreien Zwangspatienten korrelierte der Schizotypiewert mit dem Gain während der klassischen SPEM-Trials. Die Befunde weisen darauf hin, dass eine erhöhte Schizotypie einen potenziellen Endophänotyp der Zwangsstörung darstellt und sind zudem konsistent mit der wachsenden Evidenz für eine genetische Überlappung zwischen der Zwangsstörung, der Schizophrenie und gemeinsamen prädisponierenden Persönlichkeitsmerkmalen (Brainstorm Consortium et al., 2018). Die Hypothese, dass SPEM-Defizite einen Endophänotyp der Zwangsstörung darstellen könnten, erfuhr hingegen keine Konfirmation.

8.4 Impaired planning in patients with obsessive-compulsive disorder and unaffected first-degree relatives: Evidence for a cognitive endophenotype

Patienten mit Zwangsstörung zeigen eine reduzierte Planungsfähigkeit in der Turm von London (TvL)-Aufgabe. Vorläufige Evidenz für ähnliche Auffälligkeiten bei nicht affizierten erstgradigen Angehörigen von Zwangspatienten weist darauf hin, dass die reduzierte Lösungsgenauigkeit bei TvL-Problemen einen Endophänotyp der Zwangsstörung darstellen könnte. Dennoch sind die Befunde durch Inkonsistenzen gekennzeichnet, was mutmaßlich auf geringe Stichprobengrößen und die Verwendung unterschiedlicher TvL-Aufgaben zurückzuführen ist. Üblicherweise wird die Aufgabenschwierigkeit von TvL-Problemen allein anhand der zur Lösung minimal notwenigen Züge definiert. Tatsächlich bestimmen jedoch zahlreiche weitere Parameter wie die

beiden Dimensionen Suchtiefe und Zielhierarchie die kognitiven Anforderungen des TvL.

In der vorliegenden Studie wurde eine computerisierte Version des TvL verwendet, die ein 2 × 2 faktorielles Design (hohe/geringe Suchtiefe × eindeutige/teilweise ambigue Zielhierarchie) umfasste. Das Problemset wurde von *n* = 72 Zwangspatienten, *n* = 76 nicht betroffenen Angehörigen ersten Grades von Zwangspatienten und *n* = 102 gesunden Kontrollprobanden bearbeitet.

Sowohl Patienten als auch Angehörige wiesen signifikant geringere Lösungsgenauigkeiten auf als die Kontrollprobanden. Suchtiefe, Zielhierarchie und die Anzahl der zur Lösung minimal notwenigen Züge hatten keinen moderierenden Einfluss auf die Gruppenunterschiede. Ferner zeigten sich bei den Zwangspatienten keine signifikanten Effekte des Medikationsstatus, der Zwangssymptomdimensionen und der depressiven Komorbidität auf die Lösungsgenauigkeit.

Insgesamt stehen die Befunde im Einklang mit dem fronto-striatalen Modell der Zwangsstörung und stützen die Annahme, dass eine reduzierte Lösungsgenauigkeit in der TvL-Aufgabe einen aussichtsreichen Endophänotyp der Zwangsstörung darstellen könnte. Eine spezifische Ausprägung von suchtiefe- bzw. zielhierarchieassoziierten Defiziten wurde bei Zwangspatienten jedoch nicht beobachtet. Medikationsstatus, Zwangssymptomdimensionen und depressive Komorbidität hatten keinen signifikanten Einfluss auf die TvL-Performanz, was für eine Statusunabhängigkeit des Defizits bei Zwangspatienten spricht.

8.5 Impaired antisaccades in obsessive-compulsive disorder: Evidence from meta-analysis and a large empirical study

Zunehmende Evidenz weist darauf hin, dass die Zwangsstörung mit Auffälligkeiten in den CSTC Schleifen assoziiert ist. Performanzdefizite in der Antisakkadenaufgabe würden dieses Modell stützen, jedoch sind die Befunde aus den bis jetzt veröffentlichten kleinangelegten Studien weitgehend inkonsistent. Es wurden entweder erhöhte Fehlerraten, verlängerte Antisakkadenlatenzen, Auffälligkeiten in beiden oder keinem der beiden Parameter beobachtet.

Um diesen Inkonsistenzen und dem Problem der eingeschränkten Teststärke zu begegnen, wurde in der vorliegenden Studie die Antisakkadenleistung von *n* = 169 Zwangspatienten und *n* = 183 gematchten Kontrollprobanden analysiert. Da die

Antisakkadenperformanz einen potenziellen Endophänotyp der Zwangsstörung darstellt (Lennertz et al., 2012), wurden zudem n = 100 nicht affizierte Angehörige ersten Grades von Zwangspatienten untersucht. Dabei wurden neben den klassischen Parametern, Antisakkadenfehlerrate und -latenz, auch detailliertere Parameter wie die intrapersonelle Variabilität der Latenzen sowie die Rate von Fehlern mit Expresssakkadenlatenz (80–130 ms) und mit regulärer Latenz (> 130 ms) erfasst. Zudem wurden zahlreiche Einflussfaktoren inklusive des Medikationsstatus, depressiver Komorbidität, Zwangssymptomdimensionen, State-Ängstlichkeit und Schadensvermeidung als Indikator von Trait-Ängstlichkeit berücksichtigt. In einem zweiten Schritt wurde eine quantitative Metaanalyse durchgeführt, um die aktuellen Ergebnisse mit den Befunden früherer Studien in Bezug zu setzen.

In der empirischen Untersuchung zeigten Zwangspatienten verglichen mit gesunden Kontrollprobanden signifikant erhöhte Antisakkadenlatenzen, eine erhöhte intrapersonelle Variabilität der Antisakkadenlatenzen sowie eine erhöhte Antisakkadenfehlerrate. Letzterer Effekt war durch einen ausgeprägten Gruppenunterschied in der Rate von Fehlern mit Expresslatenz getrieben; bezüglich der Rate von Fehlern mit regulärer Latenz unterschieden sich die Gruppen hingegen nicht. Neben den Patienten mit Zwangsstörung zeigten auch deren Angehörige eine erhöhte Rate von Antisakkadenfehlern mit Expresslatenz und eine größere intrapersonelle Variabilität der Antisakkadenlatenzen. Medikationsstatus, depressive Komorbidität und Zwangssymptome hatten keinen signifikanten Einfluss auf die Antisakkadenperformanz der Zwangspatienten. Ferner ergaben sich innerhalb der drei Gruppen keine bedeutsamen Zusammenhänge zwischen den einzelnen Antisakkadenparametern und der State-Ängstlichkeit. Bei den Angehörigen zeigte sich jedoch eine signifikante positive Korrelation zwischen der Persönlichkeitseigenschaft Schadensvermeidung und der Antisakkadenfehlerrate. Dieser Effekt war ebenfalls durch die Rate von Fehlern mit Expresssakkadenlatenz getrieben. Die Metaanalyse ergab einen mittelgroßen Effekt für eine erhöhte Antisakkadenfehlerrate bei Zwangspatienten (SMD = 0.48, p < 0.001), während der Effekt für Antisakkadenlatenzen aufgrund starker Heterogenität nicht signifikant wurde (SMD = 0.51, p = 0.069).

Die Ergebnisse stehen im Einklang mit der Annahme einer defizitären Antisakkadenleistung bei Patienten mit Zwangsstörung, wenngleich die Effektstärken insgesamt nur moderat hoch ausfallen. Die Auswertung detaillierter Antisakkadenparameter weist dabei auf potenziell zugrundeliegende Mechanismen hin. Dass

Zwangspatienten insbesondere mehr Fehler mit Expresslatenz machen, könnte auf Defizite in der frühen, bereits vor Stimuluspräsentation erforderlichen Inhibition des superioren Colliculus zurückzuführen sein. Die Befunde stützen zudem die Rolle der Antisakkadenfehlerrate als Endophänotypenkandidat der Zwangsstörung und liefern erste Evidenz dafür, dass eine erhöhte intrapersonelle Variabilität der Antisakkadenlatenzen ebenfalls einen Endophänotyp darstellen könnte. Die bei nicht betroffenen Angehörigen beobachtete Korrelation zwischen Antisakkadenfehlerrate und Schadensvermeidung ist potenziell Ausdruck der genetischen Vulnerabilität für eine Zwangserkrankung.

9 Diskussion

In der vorliegenden Dissertation wurden verschiedene Endophänotypenkandidaten der Zwangsstörung anhand einer großen, detailliert charakterisierten Stichprobe von Zwangspatienten, deren nicht affizierten Angehörigen ersten Grades und gesunden Kontrollprobanden untersucht. Einige der potenziellen Endophänotypen zeigten sowohl bei Patienten mit Zwangsstörung als auch bei deren Angehörigen Auffälligkeiten, während andere Endophänotypenkandidaten keine Konfirmation erfuhren. Als aussichtsreiche Kandidaten erwiesen sich die Persönlichkeitseigenschaften Schadensvermeidung und Schizotypie sowie die Planungsfähigkeit in der TvL-Aufgabe, die Antisakkadenfehlerrate mit Expresslatenz und die intrapersonelle Variabilität der Antisakkadenlatenzen. Zwangspatienten, erstgradige Angehörige und Kontrollprobanden unterschieden sich hingegen nicht signifikant voneinander bezüglich ihrer volitionalen Sakkadenlatenzen sowie ihrer kontinuierlichen und prädiktiven SPEM. Für die validierten Endophänotypenkandidaten ergaben sich keine signifikanten Korrelationen mit der Schwere der Zwangssymptomatik, was auf eine Statusunabhängigkeit der endophänotypischen Auffälligkeiten hinweist. Während diese Endophänotypen mutmaßlich eine genetische Vulnerabilität widerspiegeln, tragen auch kritische Lebensereignisse im Sinne einer Gen-Umwelt-Interaktion zur Entstehung einer Zwangserkrankung bei. So berichteten Zwangspatienten in der EPOC-Studie signifikant mehr traumatische Kindheitserlebnisse als gesunde Kontrollprobanden und nicht betroffene Angehörige.

9.1 Synopsis und Integration der Endophänotypenbefunde

Die Ergebnisse der fünf Originalarbeiten, die dieser Dissertation zugrunde liegen, sind in Tabelle 4 zusammengefasst. Ferner sind dort die mit den spezifischen Endophänotypenkandidaten assoziierten Hirnregionen, Zusammenhänge mit Genvarianten, Erblichkeitsschätzungen und genetische Korrelationen mit der Zwangsstörung dargestellt.

Tabelle 4

Synopsis der in EPOC untersuchten Endophänotypenkandidaten. Dargestellt sind die in den einzelnen Originalarbeiten beobachteten Effektstärken sowie assoziierte Hirnregionen und genetische Zusammenhänge

	Stichprobe (*N*)			Effektstärken (*d*)			Genetik		
Endophänotyp	Pat.	Ang.	Kon.	Pat. vs. Kon.	Ang. vs. Kon.	Assoziierte Hirnregionen	Assoziierte Gene/SNPs	Erblichkeitsschätzung	Genetische Korrelation
Antisakkadenfehlerrate (global)	169	100	183	**0.23** [0.02, 0.44]	0.15 [-0.10, 0.39][a]	FEF, SEF, DLPFC, Basalganglien, SCi (Munoz & Everling, 2004)	GWAS: rs201048567 (Lencer et al., 2017) rs1868457 (Vaidyanathan et al., 2014) Kandidaten: RGS4SNP18 (Kattoulas et al., 2012) *RELN, GRIK4* und *HTR2A* (Greenwood et al., 2011) *NOS1AP* und *CACNG2* (Greenwood et al., 2012)	42–61 % (Greenwood et al., 2007; Malone & Iacono, 2002)	-
Antisakkadenfehlerrate (mit Expresssakkadengeschwindigkeit)	169	100	183	**0.27** [0.06, 0.48]	**0.35** [0.10, 0.59][a]	SCi, DLPFC, FEF, CN (Coe & Munoz, 2017)	-	-	-
Antisakkadenfehlerrate (mit regulärer Sakkadengeschwindigkeit)	169	100	183	0.12 [-0.08, 0.33]	0.06 [-0.18, 0.31][a]	SCi, SEF, Basalganglien (Coe & Munoz, 2017)	-	-	-
Antisakkadenlatenz	169	100	183	**0.22** [0.01, 0.43]	0.10 [-0.14, 0.35][a]	FEF, SEF, DLPFC, Basalganglien, SCi (Munoz & Everling, 2004)	-	-	-
Streuung der Antisakkadenlatenzen	169	100	183	**0.44** [0.24, 0.65]	**0.27** [0.02, 0.51][a]	FEF, SEF, DLPFC, Basalganglien, SCi (Munoz & Everling, 2004)	Kandidat: RGS4SNP18 (Kattoulas et al., 2012)	-	-

(Fortsetzung)

Tabelle 4 *(Fortsetzung)*

	Stichprobe (*N*)			Effektstärken (*d*)			Genetik		
Endo-phänotyp	Pat.	Ang.	Kon.	Pat. vs. Kon.	Ang. vs. Kon.	Assoziierte Hirnregionen	Assoziierte Gene/SNPs	Erblich-keits-schätzung	Gene-tische Korrela-tion
Klassische SPEM	168	93	171	0.13 [-0.08, 0.34]	-0.10 [-0.35, 0.15]	FEF, SEF, PEF, Cerebellum, V5 (Lencer & Trillenberg, 2008)	Kandidat: RGS4SNP4 (Kattoulas et al., 2012)	27–45 % (Hong et al., 2006; Katsanis et al., 2000)	-
Prädiktive SPEM	168	93	171	0.04 [-0.17, 0.25]	-0.17 [-0.43, 0.08]	FEF, SEF, Parietallappen, DLPFC, Cerebellum, V5, Basalganglien (Lencer et al., 2004)	Kandidat: *COMT* Val158Met (Thaker et al., 2004)	90% (Hong et al., 2006)	-
Planungs-fähigkeit (Turm von London)	72	76	102	**0.48** [0.18, 0.79]	**0.31** [0.01, 0.61][a]	DLPFC, Parietallappen, ACC, CN (van den Heuvel et al., 2005)	Kandidat: *PER3*-VNTR (Gonzáles-Giraldo et al., 2015)	-	Kognitive Perfor-manz und Zwang: 0.36 (p = .002; Brainst. Cons. et al., 2018)
Schadens-vermeidung	169	57	157	**2.02** [1.75, 2.28]	**0.85** [0.54, 1.16]	Erhöhte Konnektivität der anterioren Insula mit ACC und DLPFC (Markett et al., 2013)	Keine Evidenz aus GWAS (Service et al., 2012; Verweij et al., 2010) Kandidat: *CHRNA4* rs1044396 (Bey et al., 2016)	42–57 % (Garcia et al., 2013; Gillespie et al., 2003; Keller et al., 2005)	Neuroti-zismus und Zwang: 0.29 (p = 5.58 × 10^{-5}; Brainst. Cons. et al., 2018)
Schizotypie	166	93	170	**1.13** [0.90, 1.36]	**0.52** [0.26, 0.78]	Reduzierte graue Substanz im MPFC, OFC und temporalen Cortex (Ettinger et al., 2012) Reduzierte graue Substanz in der Insula und im DLPFC (Wang et al., 2015)	Kandidaten: *COMT* Val158Met (Avramo-poulos et al., 2002; Stefanis et al., 2004) rs760761, rs2619522 und rs1018381 (Stefanis et al., 2007) rs1344706 (Yasuda et al., 2011)	30–50 % (Ericson et al., 2011; Lin et al., 2007; Linney et al., 2003; Kendler & Hewitt, 1992)	-
Volitionale Sakkaden-latenz	115	31	103	-0.01 [-0.28, 0.26]	0.12 [-0.28, 0.53][a]	SMC, ACC, DLPFC, Parietallappen, Basalganglien (Krieghoff et al., 2011)	-	-	-

Anmerkung: Fettgedruckte Effektstärken sind signifikant (p < .05). In Klammern ist das 95 %-Konfidenzintervall der jeweiligen Effektstärke angegeben. ACC, anteriorer cingulärer Cortex; Ang., erstgradige Angehörige von Zwangspatienten; CN, Nucleus caudatus; DLPFC, dorsolateraler präfrontaler Cortex; FEF, frontales Augenfeld; Kon., Kontrollprobanden; MPFC, medialer frontaler Cortex; OFC, orbitofrontaler Cortex; Pat., Zwangspatienten; PEF, parietales Augenfeld; SCi, superiorer Colliculus internus; SEF, supplementäres Augenfeld; SMC, supplementärmotorischer Cortex; SPEM, langsame Augenfolgebewegungen.
[a] Die Effektstärken wurden jeweils basierend auf einer ANCOVA unter Berücksichtigung des Alters als Kovariate berechnet.

Die größten Effektstärken ergaben sich für die Persönlichkeitseigenschaften Schadensvermeidung und Schizotypie. Hier zeigten sich jeweils deutlich höhere Werte bei Zwangspatienten als bei Kontrollprobanden sowie moderat erhöhte Werte bei Angehörigen. Mittlere Effektstärken resultierten für die Planungsfähigkeit im TvL, die Streuung der Antisakkadenlatenzen und die Antisakkadenfehlerrate mit Expresslatenz. Während bezüglich dieser Parameter sowohl Zwangspatienten als auch deren nicht affizierte Angehörige signifikant erhöhte Werte aufwiesen, ergaben sich für die globale Antisakkadenfehlerrate sowie für die Antisakkadenlatenz nur bei Zwangspatienten moderate Auffälligkeiten im Vergleich zu Kontrollprobanden, bei Angehörigen jedoch nicht. Zudem zeigte sich innerhalb der Gruppe der Angehörigen eine signifikante Korrelation zwischen den beiden Endophänotypenkandidaten Schadensvermeidung und Antisakkadenfehlerrate mit Expresslatenz, was vor dem Hintergrund einer angenommenen Pleiotropie darauf hinweist, dass beiden Merkmalen ähnliche Pathomechanismen zugrunde liegen könnten, in denen sich das genetische Zwangsstörungsrisiko niederschlägt (vgl. Abbildung 2). Hinsichtlich der klassischen und prädiktiven SPEM sowie der volitionalen Sakkaden unterschieden sich die drei Gruppen hingegen nicht signifikant voneinander.

Über potenzielle hirnphysiologische Mechanismen, die die beobachteten Auffälligkeiten auf der Verhaltensebene mediieren, können Befunde aus MRT-Studien Aufschluss geben. Eine reduzierte graue Substanz im OFC ist beispielweise sowohl mit erhöhter Schizotypie (Ettinger et al., 2012) als auch mit der Zwangsstörung selbst assoziiert (van den Heuvel et al., 2009; obgleich die Befunde hinsichtlich der Richtung des Zusammenhangs nicht gänzlich konsistent sind, siehe Piras et al., 2015). Die Basalganglien, die eine zentrale Rolle im fronto-striatalen Modell der Zwangsstörung spielen, sind mit mehreren Endophänotypen assoziiert, darunter die verschiedenen Antisakkadenparameter und die Planungsfähigkeit im TvL. Andere Kandidaten, die ebenfalls durch eine verstärkte Rekrutierung der Basalganglien gekennzeichnet sind, wie die Ausführung von SPEM und volitionalen Sakkaden, erfuhren in EPOC jedoch keine Konfirmation als aussichtsreiche Endophänotypen. Dies legt die Vermutung nahe, dass insbesondere die interferierenden Aufgabenmerkmale und die resultierenden mehrdeutigen Handlungstendenzen, durch die sich Antisakkaden und TvL gegenüber SPEM und volitionalen Sakkaden auszeichnen, sensitiv für die kognitiven Defizite von Zwangspatienten sind.

Bei der Interpretation der Befunde ist weiterhin zu berücksichtigen, dass die Pathophysiologie der Zwangsstörung nicht ausschließlich auf die CSTC beschränkt ist. Eine kürzlich veröffentlichte Metaanalyse von 18 Resting-State-MRT-Studien erbrachte sowohl Evidenz für das fronto-striatale Modell der Zwangsstörung als auch für das sogenannte Tripel-Netzwerk-Modell, das von einem aberranten Zusammenspiel des Salienznetzwerks (SAL), des DMN und des fronto-parietalen Netzwerks (FPN) ausgeht (Gürsel, Avram, Sorg, Brandl, & Koch, 2018). Während eine erhöhte Aktivität im DMN mit selbstreferenziellen Gedanken assoziiert ist, ist das FPN von zentraler Relevanz für die Ausführung von zielgerichtetem Verhalten. Das antagonistische Zusammenspiel von DMN und FPN wird dabei vom SAL moduliert. Das SAL fungiert also als eine Art Schalter, der zwischen DMN und FPN hin- und herschaltet (Menon, 2011; Sridharan, Levitin, & Menon, 2008). Die für Zwangspatienten charakteristische Schwierigkeit, von Zwangsgedanken auf zielgerichtetes Verhalten umzuschalten, können durch eine dysfunktionale Interaktion zwischen diesen drei Netzwerken mitbedingt sein (Gürsel et al., 2018). Ebenso könnten sich auch endophänotypische Auffälligkeiten auf Basis des Tripel-Netzwerk-Modells erklären lassen. Eine hohe Schadensvermeidungsneigung geht beispielsweise einerseits mit einer erhöhten Konnektivität zwischen Insula und ACC einher, anderseits mit einer gesteigerten Konnektivität zwischen Insula und DLPFC (Markett et al., 2013). ACC und Insula stellen dabei die wesentlichen Komponenten des SAL dar, während der DLPFC ins FPN involviert ist (Gürsel et al., 2018). Insgesamt scheinen die Zusammenhänge zwischen hirnphysiologischen und neuropsychologischen Auffälligkeiten bei Zwangspatienten komplex zu sein, weshalb es weiterer Forschungsbestrebungen bedarf, die die verschiedenen Untersuchungsebenen simultan erfassen. Die anstehende Auswertung der in EPOC erhobenen Bildgebungsdaten könnte in dieser Hinsicht aufschlussreich sein.

Inwiefern sich die validierten Endophänotypenkandidaten als wertvoll für die Erforschung der genetischen Grundlage der Zwangsstörung erweisen, ist insbesondere von ihrer Erblichkeit und der genetischen Korrelation mit der Zwangsstörung abhängig. Wenngleich noch nicht für alle hier untersuchten Endophänotypenkandidaten Heritabilitätsschätzungen vorliegen, fallen sie insgesamt ähnlich hoch aus wie für die Zwangsstörung selbst. Lediglich für die prädiktiven SPEM wird basierend auf einer Untersuchung von Schizophreniepatienten und deren Geschwistern eine enorme Heritabilität von 90 % berichtet (Hong et al., 2006). Da die EPOC-Befunde die

Rolle prädiktiver SPEM als Endophänotyp der Zwangsstörung jedoch nicht stützen, ist ihr Nutzen für die Detektion zwangsassoziierter Genorte beschränkt. Ferner liegen bis jetzt nur wenige genomweite Studien vor, in denen die genetische Grundlage potenzieller Endophänotypen exploriert wurde. In einer GWAS von 17 psychophysiologischen Parametern ergaben sich lediglich für zwei Maße genomweit signifikante Assoziationen (Iacono et al., 2014), darunter bemerkenswerterweise die Antisakkadenfehlerrate (Vaidyanathan et al., 2014). Der SNP rs1868457 erklärte dabei 0.67 % der Varianz in der Fehlerrate ($p = 3.3 \times 10^{-9}$), wobei die Autoren einräumen, dass dieser Wert zweifelsohne einer Inflation durch den „winner's curse"-Mechanismus unterliegt (Iacono, Malone, & Vrieze, 2017; Ioannidis, 2008). Lencer et al. (2017) fanden für die Antisakkadenfehlerrate ebenfalls eine genomweit signifikante Assoziation; der Befund von Vaidyanathan et al. (2014) konnte jedoch nicht repliziert werden. Für alle weiteren in EPOC untersuchten Endophänotypenkandidaten wurden bis jetzt nur Zusammenhänge mit Kandidatengenen beobachtet. Beispielsweise ist das Val-Allel des *COMT* Val158Met Polymorphismus sowohl mit einer erhöhten Schizotypie (Avramopoulos et al., 2002; Stefanis et al., 2004) als auch mit schlechteren prädiktiven SPEM bei gesunden Kontrollprobanden assoziiert (bei Schizophreniepatienten zeigte sich allerdings ein entgegengesetzter Zusammenhang im Sinne besserer SPEM bei Vorliegen eines Val-Allels; Thaker et al., 2004). Taylor (2013) fand in seiner Metaanalyse von Kandidatengenen zudem einen signifikanten Zusammenhang zwischen dem *COMT* Val158Met Polymorphismus und der Zwangsstörung. Jedoch ging dabei das Met-Allel mit einem erhöhten Risiko einher und der Effekt beschränkte sich auf männlichen Probanden (Taylor, 2013). Vor dem Hintergrund der ebenfalls metaanalytisch validierten Assoziation zwischen der Diagnose Zwangsstörung und dem *HTR2A*-Gen (Taylor, 2013) erscheint es ferner interessant, dass auch die Antisakkadenfehlerrate in einer Stichprobe von Schizophreniepatienten und deren Familienangehörigen einen signifikanten Zusammenhang mit diesem Gen aufwies (Greenwood et al., 2011). Einschränkend ist jedoch zu sagen, dass die Effekte jeweils unterschiedliche SNPs innerhalb des *HTR2A*-Gens betreffen, die nicht gekoppelt vererbt werden. Obgleich also vereinzelt Überschneidungen zwischen zwangsassoziierten und endophänotypassoziierten Genorten auszumachen sind, beschränken sich diese bislang auf klassische Kandidatengene und sind hinsichtlich der Richtung der Zusammenhänge oder der spezifischen SNPs durch Inkonsistenzen gekennzeichnet.

Ein empirisches Maß zur Bewertung des wissenschaftlichen Nutzens einzelner Endophänotypen stellt der *Endophenotype Ranking Value* (*ERV*) dar, der auf einer Schätzung der standardisierten genetischen Kovarianz zwischen einem Endophänotypenkandidaten und einer spezifischen Erkrankung basiert (Glahn et al., 2012). Formal ist er definiert als

$$ERV_{ie} = |\sqrt{h_i^2}\sqrt{h_e^2}\,\rho_g|,$$

wobei h_i^2 die Heritabilität einer Erkrankung i, h_e^2 die Heritabilität eines Endophänotyps e und ρ_g ihre genetische Korrelation beschreiben. Der *ERV* kann Werte zwischen 0 und 1 annehmen, wobei hohe Werte indizieren, dass sowohl Endophänotyp als auch Erkrankung hocherblich sind und ihnen geteilte genetische Faktoren zugrunde liegen. Ein Vorteil des *ERV*-Ansatzes besteht darin, dass eine große Anzahl von Endophänotypenkandidaten effizient klassifiziert werden kann, bevor weitere molekulargenetische Analysen durchgeführt werden (Glahn et al., 2012). Allerdings setzt die Berechnung des *ERV* voraus, dass sowohl die Heritabilitäten als auch die genetische Korrelation zwischen potenziellem Endophänotyp und Erkrankung bekannt sind. Während für die Zwangsstörung und einen Großteil der in EPOC untersuchten Endophänotypenkandidaten reliable Heritabilitätsschätzungen vorliegen, sind deren genetische Korrelationen noch weitgehend unerforscht. Bis jetzt wurde im Rahmen des Brainstorm-Projektes lediglich die genetische Überlappung der Zwangsstörung mit einem globalen kognitiven Performanzmaß untersucht (Brainstorm Consortium et al., 2018). Es resultierte eine moderate positive Korrelation (r = 0.36), die nominal signifikant war, einer Korrektur für multiples Testen jedoch nicht standhielt. Vor dem Hintergrund, dass die Zwangsstörung phänotypisch mit kognitiven Defiziten assoziiert ist, erscheint die positive genetische Korrelation kontraintuitiv. Analysen spezifischerer kognitiver Funktionen sind notwendig, um diesen Befund zu stützen und näher zu explorieren. Im Brainstorm-Projekt wurde zudem eine signifikante genetische Korrelation zwischen der Zwangsstörung und Neurotizismus beobachtet (r = 0.29; Brainstorm Consortium et al., 2018). Dies ist konsistent mit dem Befund, dass sowohl Zwangspatienten als auch deren erstgradige Angehörige eine erhöhte Ausprägung der mit Neurotizismus eng verwandten Persönlichkeitseigenschaft Schadensvermeidung aufweisen (Ettelt et al., 2008; EPOC-Befunde).

9.2 Worin besteht der Nutzen des Endophänotypenansatzes?

Ein vielfach am Endophänotypenansatz geäußerter Kritikpunkt ist, dass die diskutierten Endophänotypenkandidaten oft Heritabilitäten aufweisen, die nicht größer sind als die des dichotomen diagnostischen Phänotyps, mit dem sie assoziiert sind. Auch die Zusammenhänge zwischen spezifischen Genvarianten und den potenziellen Endophänotypen scheinen insgesamt nicht stärker zu sein als deren Assoziationen mit klassischen Krankheitsphänotypen. So zeigte sich in einer Metaanalyse von Flint und Munafò (2006), dass die Effektstärken der Zusammenhänge des *COMT* Val158Met Genotyps mit verschiedenen Endophänotypenkandidaten der Schizophrenie – der Performanz im Wisconsin Card Sorting Test, im N-Back-Test sowie der P300-Amplitude und -Latenz – sehr gering und weitgehend nicht signifikant sind. Dies werten die Autoren als Hinweis darauf, dass die genetische Architektur potenzieller Endophänotypen entgegen früheren Vermutungen nicht weniger komplex ist als die distaler Krankheitsphänotypen. Ferner zeigen die Verteilungen genetischer Effektstärken keine bedeutsamen Unterschiede zwischen physiologischen und behavioralen Phänotypen (Flint, Valdar, Shifman, & Mott, 2005). Eine detaillierte Analyse der genetischen Grundlage komplexer physiologischer, biochemischer, anatomischer und verhaltensbezogener Merkmale bei Mäusen ergab, dass die meisten Genloci jeweils nur einen geringen Anteil der phänotypischen Varianz erklärten. Lediglich 10 der untersuchten 843 QTLs wiesen eine Varianzaufklärung von mehr als 5 % auf; der Durchschnitt lag bei 2.2 % (Valdar et al., 2006). Humanstudien gehen von noch deutlich geringeren Effekten aus. Die durchschnittliche Varianzaufklärung von fast 700 genomweit mit der Körpergröße assoziierten Varianten, die eines der am genausten messbaren und am höchsten erblichen Merkmale des Menschen darstellt, liegt bei etwa 0.03 % (Wood et al., 2014). Die größte in einer GWAS komplexer Phänotypen zu erwartende Effektstärke eines einzelnen SNPs entspricht einer Varianzaufklärung von etwa 0.5 % (Iacono et al., 2017), was einmal mehr auf die Notwendigkeit hinreichend großer Stichproben hinweist.

Basierend auf diesen Befunden wird argumentiert, dass durch die Untersuchung von behavioralen oder hirnphysiologischen Endophänotypenkandidaten auch keine bessere Aussicht auf die Identifizierung von Suszeptibilitätsgenen zu erwarten ist. Ihre genetische Architektur ist voraussichtlich ebenso komplex wie die klassischer Krankheitsphänotypen und wird mutmaßlich durch viele tausend Varianten innerhalb verschiedener Gene beeinflusst, die einzeln jeweils nur eine sehr geringe Effektstärke

aufweisen (Iacono et al., 2017). Dennoch bieten Endophänotypen eine Vielzahl von Vorteilen in Gen-Mapping-Studien, selbst wenn ihre Heritabilitäten ähnlich hoch oder geringer ausfallen als die der mit ihnen assoziierten Erkrankung (Glahn et al., 2014). Insbesondere ist die Teststärke für quantitative Phänotypen immer höher als für dichotome Merkmale, da sie sowohl innerhalb der Gruppe erkrankter Personen zwischen geringer und stärker betroffenen differenzieren als auch innerhalb der Gruppe gesunder Personen zwischen jenen mit höherem und geringerem Risiko (Blangero, Williams, & Almasy, 2003; Williams & Blangero, 2004). Ein noch beträchtlicherer Anstieg der Teststärke kann durch einen multivariaten Ansatz erzielt werden, bei dem dichotome diagnostische Phänotypen und die mit ihnen assoziierten quantitativen Endophänotypen kombiniert analysiert werden (Glahn et al., 2012; 2014; Liu, Pei, Papasian, & Deng, 2009; O'Reilly et al., 2012; Yuan & Diao, 2011). Ebenso könnte die gleichzeitige Berücksichtigung verschiedener Endophänotypen die Identifikation von Risikogenen erleichtern. Darüber hinaus erscheint es aussichtsreich, Endophänotypenkandidaten zu explorieren, die noch direkter am Wirkungsort der Gene liegen, wie beispielsweise genetische Transkripte (Glahn et al., 2012; 2014). Insgesamt werden Studien, in denen mit Endophänotypen assoziierte Genvarianten identifiziert werden sollen, allerdings auf extrem große Stichproben angewiesen sein, was am besten durch die Bildung von Konsortien und Data Sharing zu realisieren ist (Iacono et al., 2017).

Eine weitere Diskussionsfrage betrifft die Spezifität von Endophänotypen. Da in EPOC keine Patientenkontrollgruppe erhoben wurde, kann anhand der vorliegenden Daten nicht beurteilt werden, ob die beobachteten Auffälligkeiten spezifisch für Zwangspatienten sind oder auch bei anderen psychiatrischen Erkrankungen vorliegen. Störungsspezifität ist jedoch kein Definitionskriterium eines Endophänotyps. Im Gegenteil schließen Endophänotypen auch Merkmale ein, die sensitiv für multiple diagnostische Konstrukte sind und so zur Identifikation geteilter Pathomechanismen beitragen können (Glahn et al., 2014). Eine konkrete Erkrankung kann mutmaßlich mit zahlreichen Endophänotypen assoziiert sein, während ein bestimmter Endophänotyp ebenso mit mehreren Diagnosen zusammenhängen kann (Cannon & Keller, 2006). In einer Übersichtsarbeit war die Hälfte der untersuchten 36 Endophänotypen mit drei bis sieben verschiedenen Erkrankungen assoziiert und die meisten Erkrankungen mit multiplen Endophänotypen (Iacono et al., 2017). Traditionell als distinkt konzeptualisierte Störungsbilder zeigen zudem deutliche Überlappungen hinsichtlich ihrer

genetischen und neurophysiologischen Grundlagen (Beauchaine & Constantino, 2017; Brainstorm Consortium et al., 2018; Zisner & Beauchaine, 2016), worin zum Ausdruck kommt, dass diagnostische Grenzen nicht mit biologischen Grenzen gleichzusetzen sind. Die Zwangsstörung weist beispielsweise signifikante genetische Korrelationen mit der Schizophrenie, dem Tourette-Syndrom, der Anorexie und der bipolaren Störung auf (Brainstorm Consortium et al., 2018; Tylee et al., 2016).

Diese und weitere Befunde aus der störungsübergreifenden Forschung bilden den Ausgangspunkt des Research Domain Criteria (RDoC)-Projektes, das anstrebt, die Klassifikation psychiatrischer Erkrankungen basierend auf Dimensionen beobachtbaren Verhaltens und neurobiologischer Messwerte neu zu gestalten (Cuthbert & Insel, 2010). RDoC betonen kontinuierliche biobehaviorale Dimensionen im Gegensatz zur klassischen kategorialen Einteilung. Sie nutzen Erkenntnisse aus Neurowissenschaften, Genomik und Verhaltenswissenschaften, um Einsicht in psychopathologierelevante dimensionale Konstrukte zu erhalten. Durch den Beitrag zu einem verbesserten integrativen Verständnis von Psychopathologien zielt der RDoC-Ansatz zudem darauf ab, die Entwicklung neuer und effektiverer Behandlungen zu fördern (Simmons & Quinn, 2014). Aus der RDoC-Perspektive stellen Endophänotypen prinzipiell reinere und konstruktvalidere Indikatoren biologischer Systeme dar, weshalb sie die klassischen symptombasierten Diagnosen im Forschungskontext weitestgehend ersetzen sollen. Die transdiagnostische Konzeptualisierung der RDoC steht ebenfalls in Einklang mit der Beobachtung, dass viele Endophänotypen störungsübergreifend zu sein scheinen (Lilienfeld, 2014; Miller & Rockstroh, 2013). Vor diesem Hintergrund sind Endophänotypen insbesondere auch von klassischen Biomarkern abzugrenzen, die sensitive und spezifische Indikatoren einer Störung darstellen und vor allem diagnostischen Wert haben (Hasler, Drevets, Gould, Gottesman, & Manji, 2006). Der Nutzen von Endophänotypen besteht hingegen in ihrem Beitrag zur Identifikation von Risikogenen, Störungsmechanismen und transdiagnostischen ätiologischen Faktoren. Ferner erhofft sich die Forschung, dass Endophänotypen als prospektive Indikatoren einer Vulnerabilität für psychiatrische Erkrankungen genutzt werden und so deren Prävention verbessern können (Beauchaine, 2009; Gottesman & Gould, 2003; Iacono, 2018).

9.3 Diskussion der inkonsistenten Befundlage früherer Studien

Die inkonsistenten Befunde früherer Studien, in denen potenzielle Endophänotypen der Zwangsstörung untersucht wurden, scheinen insbesondere durch geringe Stichprobengrößen, variierende Taskdesigns und die unzureichende Berücksichtigung klinischer Stichprobencharakteristika bedingt zu sein. Diesen Einschränkungen begegnet die EPOC-Studie insofern, als sie eine der bislang größten tief phänotypisierten Stichproben von Zwangspatienten, nicht betroffenen Angehörigen und Kontrollprobanden umfasst. Neben den verschiedenen kognitiven Performanzmaßen wurden zahlreiche klinische Variablen wie Komorbiditäten, Symptomdimensionen, Schweregrad und Störungsbeginn der Zwangserkrankung erhoben und in den Analysen berücksichtigt. Ferner wurden elaborierte Taskdesigns verwendet, die basierend auf vorherigen Studien als besonders sensitiv für Gruppenunterschiede zwischen Zwangspatienten und Kontrollprobanden eingestuft worden waren.

Der verglichen mit vorherigen Untersuchungen große Stichprobenumfang der EPOC-Studie ermöglicht eine hohe statistische Teststärke. Dies ist insbesondere im Hinblick auf den Gesichtspunkt essentiell, dass bei Angehörigen nur subtile Auffälligkeiten zu erwarten sind, deren Detektion einer ausreichenden Stichprobengröße bedarf (Glahn et al., 2014). Da mutmaßlich einige, aber nicht alle Angehörigen ein erhöhtes genetisches Risiko aufweisen, sind für sie Ausprägungen zu erwarten, die etwa in der Mitte zwischen Patienten und gesunden Kontrollprobanden liegen (Iacono et al., 2017). Im Sinne des Probabilismus wird außerdem angenommen, dass nicht alle Patienten Endophänotypen zeigen und zugleich nicht alle Personen mit endophänotypischen Defiziten Symptome einer psychiatrischen Erkrankung aufweisen (Gould & Gottesman, 2006), was ebenfalls zur genuinen Einschränkung der Gruppenunterschiede beiträgt und auf die Notwendigkeit hinreichend großer Stichproben hinweist.

Weiterhin könnte die Heterogenität der Zwangsstörung zu den inkonsistenten Befunden früherer Studien beigetragen haben. Da die einzelnen Symptomdimensionen mit verschiedenen kognitiven und neurophysiologischen Auffälligkeiten einhergehen (siehe Kapitel 6), ist zu erwarten, dass studienübergreifende Unterschiede in der Stichprobenzusammensetzung hinsichtlich der Symptomdimensionsausprägungen einen Beitrag zur inkonsistenten Befundlage geleitestet haben. Die EPOC-Ergebnisse stützen die Annahme eines engen Zusammenhangs zwischen kognitiven Auffälligkeiten und Symptomdimensionen jedoch nur bedingt. Zwar

ergaben sich in einigen Analysen nominal signifikante Korrelationen zwischen den symptomspezifischen Faktorwerten und den jeweiligen Performanzmaßen, einer Korrektur für multiples Testen hielten sie zumeist jedoch nicht stand. Lediglich die Persönlichkeitseigenschaft Schadensvermeidung korrelierte signifikant positiv mit der Ausprägung der Symptomdimensionen Zwangsgedanken/Kontrollzwänge und Waschzwänge/Kontamination, nicht jedoch mit Symmetrie/Ordnung und Horten. Dies könnte darauf hinweisen, dass eine erhöhte Schadensvermeidungsneigung insbesondere zur Entstehung von Wasch- und Kontrollzwängen prädisponiert. Die Befunde sind dabei konsistent mit den Bewertungsmustern, die den spezifischen Zwangssymptomen zugrunde liegen. Während Symmetrie- und Ordnungszwänge oftmals mit einem „not just right"-Gefühl einhergehen (Coles, Frost, Heimberg, & Rhéaume, 2003), steht bei Kontroll- und Waschzwängen die Verhinderung eines antizipierten Schadens deutlicher im Fokus. Zur Klärung der genauen ätiologischen Mechanismen bedarf es jedoch Längsschnittstudien, die den zeitlichen Verlauf der prädisponierenden Persönlichkeitseigenschaften im Zusammenhang mit den einzelnen Symptomdimensionen der Zwangsstörung untersuchen.

Weitere klinische Variablen wie die Medikation mit Antidepressiva, State-Ängstlichkeit, depressive Komorbiditäten und die Zwangssymptomschwere hatten keinen signifikanten Einfluss auf die exekutiven Fähigkeiten. Dieser Befund steht im Einklang mit den Ergebnissen dreier Metaanalysen (Abramovitch et al., 2013; Shin, Lee et al., 2014; Snyder et al., 2015) und ist zudem konsistent mit dem Endophänotypenkriterium der Statusunabhängigkeit.

9.4 Limitationen der EPOC-Studie

Die vorliegende Arbeit weist einige Limitationen auf. Zum einen sind die erstgradigen Angehörigen in der Gesamtstichprobe sowie auch in den Teilstichproben, die in den fünf Originalarbeiten analysiert wurden, signifikant älter als die Zwangspatienten und Kontrollprobanden. Da das Alter einen wesentlichen Einfluss auf kognitive Leistungsparameter wie die Antisakkadenlatenz und -fehlerrate hat, ist es von zentraler Wichtigkeit, diesem Effekt Rechnung zu tragen. In den Originalarbeiten geschah dies einerseits dadurch, dass das Alter als Kovariate in das statistische Modell mitaufgenommen wurde, wenn Gruppenunterschiede zwischen Angehörigen und Kontrollen oder Patienten analysiert wurden. Andererseits wurden die Ergebnisse in Substichproben überprüft, die hinsichtlich des Alters gematcht waren. Die

Berücksichtigung des Alters als Kovariate ist zulässig, da das Alter kein inhärent gruppentrennendes Merkmal darstellt, das heißt die Population der Angehörigen von Zwangspatienten nicht grundsätzlich älter ist als die Population der Kontrollprobanden (Miller & Chapman, 2001). Der Gruppenunterschied im Alter ist lediglich darauf zurückzuführen, dass mehr Elternteile von Zwangserkrankten rekrutiert werden konnten als volljährigen Kinder oder Geschwister. Dennoch bleibt anzumerken, dass die Berücksichtigung des Alters als Kovariate zu einer Reduktion der statistischen Teststärke beigetragen haben kann, sodass die Größe der Gruppeneffkte mutmaßlich leicht unterschätzt wurde.

Eine weitere Limitation der EPOC-Studie besteht darin, dass ein Großteil der Patienten mediziert war. Die Medikation beschränkte sich jedoch auf SSRI und andere Antidepressiva, die im Gegensatz zu Benzodiazepinen keinen negativen Einfluss auf verschiedene kognitive Leistungsparameter (Shin, Lee et al., 2014) und die Antisakkadenperformanz zu haben scheinen (Green, King, & Trimble, 2000). Dennoch ist zu berücksichtigen, dass sich die Medikation mit Psychopharmaka in Veränderungen der funktionellen Hirnnetzwerke (Shin, Jung et al., 2014) sowie der corticalen Dicke niederschlagen kann (Boedhoe et al., 2017). Um den Einfluss der Psychopharmakaeinnahme auf die jeweiligen exekutiven Fähigkeiten zu untersuchen, wurden in den einzelnen Originalarbeiten aktuell medizierte, früher medizierte und medikationsnaive Patienten miteinander verglichen. Hier zeigten sich in keiner der Analysen signifikante Effekte.

9.5 Ausblick

Die Endophänotypenkandidaten, die in der vorliegenden Arbeit insofern Konfirmation erfahren haben, als sie sowohl bei Zwangspatienten als auch bei deren nicht affizierte Angehörigen beobachtet wurden, können einen wichtigen Beitrag zur Klärung der Ätiologie der Zwangsstörung und zur Identifikation von Suszeptibilitätsgenen leisten. Es bleibt jedoch zu betonen, dass es sich weiterhin lediglich um Kandidaten handelt, die die Eingangskriterien eines Endophänotyps erfüllen, molekulargenetisch jedoch noch zu validieren sind (Iacono et al., 2017). Zeigen sie eine robuste Assoziation mit spezifischen Genvarianten? Und sind diese Varianten wiederum replizierbar mit dem klinischen Phänotyp assoziiert? Die höchste Stufe der Konstruktvalidierung umfasst nach Iacono et al. (2017) schließlich den Nutzen eines Endophänotyps für Forschung und Therapie. Hierzu zählen unter anderem die

Vorhersage des klinischen Verlaufs und das verbesserte Verständnis der neuronalen Mechanismen, die interindividuellen Unterschieden in einem Endophänotyp zugrunde liegen.

Nach Abschluss der Genotypisierung aller EPOC-Probanden sollen polygene Risikoscores (PRS), die das genetische Risiko für eine Zwangsstörung widerspiegeln, basierend auf der aktuellen Meta-GWAS (IOCDF-GC & OCGAS, 2017) berechnet werden. Im Sinne einer erfolgreichen Validierung sollten diese PRS in der Gruppe der Zwangspatienten am höchsten und bei den Kontrollprobanden am niedrigsten ausfallen, während für Angehörige eine mittlere Ausprägung zu erwarten ist. Anschließend sollen die PRS mit den verschiedenen Endophänotypen korreliert werden, um zu überprüfen, ob diejenigen genetischen Varianten, die das Zwangsstörungsrisiko vermitteln, auch mit den potenziellen Endophänotypen assoziiert sind. Darüber hinaus sollen die EPOC-Daten in die nächste GWAS des Psychiatric Genomic Consortium (PGC) eingeschlossen werden, die voraussichtlich mehr als 30,000 Patientendaten umfassen wird. Da die erwartete Anzahl an genomweit signifikanten Signalen ab einer kritischen Stichprobengröße zunächst exponentiell und dann linear zunimmt, ist davon auszugehen, dass bald die ersten genomweit signifikant mit der Zwangsstörung assoziierten SNPs identifiziert werden (Sullivan et al., 2017).

Weiterhin ist zu berücksichtigen, dass Endophänotypen denselben Gen × Umwelt-Interaktionen wie traditionelle kategoriale Diagnosen unterliegen, sodass auch die Assoziationen zwischen Endophänotypen und spezifischen Genvarianten über epigenetische Mechanismen moduliert werden. Aufgrund dessen könnten die Zusammenhänge zwischen Genen und Endophänotypen über die Lebensspanne variieren (Iacono et al., 2017). Da die Genexpression dynamisch ist, ist die Berücksichtigung von Alter und Entwicklungsstand möglicherweise wichtig für die Identifikation von endophänotypassoziierten Genvarianten. Frühere Entwicklungsperioden sind durch eine flachere „epigenetische Landschaft“ gekennzeichnet, sodass Abweichungen in der Entwicklungstrajektorie leichter möglich sind als in späteren Perioden, wenn die Pfade bereits stärker kanalisiert sind (Waddington, 1956). Longitudinale Designs könnten in diesem Kontext besonders aufschlussreich sein, weshalb die EPOC-Daten im Rahmen eines Folgeprojektes um einen zweiten Messzeitpunkt erweitert werden sollen. Zur Untersuchung epigenetischer Mechanismen sollen außerdem genomweite Methylierungsanalysen durchgeführt werden.

Darüber hinaus liegen von fast allen Probanden neben DNA- auch RNA-Proben vor, auf deren Basis die Expressionsrate spezifischer Gene analysiert werden kann.

9.6 Fazit

Insgesamt konnten im Rahmen der vorliegenden Dissertation verschiedene Endophänotypenkandidaten der Zwangsstörung validiert werden. Sowohl Patienten als auch deren erstgradige Angehörige zeigten gegenüber gesunden Kontrollprobanden Auffälligkeiten in der Planungsfähigkeit, der Rate von Antisakkadenfehlern mit Expresssakkadenlatenz, der intrapersonellen Variabilität der Antisakkadenlatenzen sowie hinsichtlich der Persönlichkeitseigenschaften Schadensvermeidung und Schizotypie. Die Befunde stehen im Einklang mit dem fronto-striatalen Modell der Zwangsstörung und können als Ansatzpunkt für die Erforschung konkreter Störungsmechanismen dienen. Die GWAS-Ära ist nicht nur durch die Identifikation von Risikogenen gekennzeichnet, sondern ebenso durch die Entdeckung von Phänotypen und durch ihre Rekonzeptualisierung als vielschichtige Konstellationen von Messwerten (Bilder, 2008). Darauf basierende transdiagnostische Ansätze haben aussichtsreiche Implikationen für die zukünftige Klassifikation psychiatrischer Erkrankungen und deren Therapie (Robbins et al., 2012). Schlussendlich könnte der primäre Nutzen von Endophänotypen nicht wie anfänglich postuliert in der Identifikation von Risikogenen liegen, sondern vielmehr in ihrem Beitrag zum Verständnis konkreter psychopathologischer Mechanismen (Iacono et al., 2017).

Literaturverzeichnis

Abramovitch, A., Abramowitz, J. S., & Mittelman, A. (2013). The neuropsychology of adult obsessive–compulsive disorder: a meta-analysis. *Clinical Psychology Review, 33*(8), 1163–1171.

Abramovitch, A., & Cooperman, A. (2015). The cognitive neuropsychology of obsessive-compulsive disorder: a critical review. *Journal of Obsessive-Compulsive and Related Disorders*, 5, 24–36.

Adhikari, B. M., Jahanshad, N., Shukla, D., Glahn, D. C., Blangero, J., Reynolds, R. C., ... & Kochunov, P. (2018). Heritability estimates on resting state fMRI data using ENIGMA analysis pipeline. *Pacific Symposium on Biocomputing, 23*, 307–318.

Ahmari, S. E., Spellman, T., Douglass, N. L., Kheirbek, M. A., Simpson, H. B., Deisseroth, K., ... & Hen, R. (2013). Repeated cortico-striatal stimulation generates persistent OCD-like behavior. *Science, 340*(6137), 1234–1239.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences, 13*(7), 266–271.

Alonso, P., Cuadras, D., Gabriëls, L., Denys, D., Goodman, W., Greenberg, B. D., ... & Menchon, J. M. (2015). Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PloS One, 10*(7), e0133591.

Alvarenga, P. G., do Rosário, M. C., Batistuzzo, M. C., Diniz, J. B., Shavitt, R. G., Duran, F. L., ... & Hoexter, M. Q. (2012). Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naïve patients. *Journal of Psychiatric Research, 46*(12), 1635–1642.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Arlington, VA: American Psychiatric Association Publishing.

Andersen, R. A. (1997). Multimodal integration for the representation of space in the posterior parietal cortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 352*(1360), 1421–1428.

Arnsten, A. F., & Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(4), 356–367.

Avramopoulos, D., Stefanis, N. C., Hantoumi, I., Smyrnis, N., Evdokimidis, I., & Stefanis, C. N. (2002). Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. *Molecular Psychiatry, 7*(7), 706–711.

Baer, L (1994). Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. *The Journal of Clinical Psychiatry, 55*, 18–23.

Barkley, R. A., Murphy, K. R., & Fischer, M. (2008). *ADHD in adults: what the science tells us.* New York, NY: Guilford.

Barrantes-Vidal, N., Grant, P., & Kwapil, T. R. (2015). The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophrenia Bulletin, 41*(suppl_2), S408–S416.

Baxter Jr, L. R., Schwartz, J. M., Mazziotta, J. C., Phelps, M. E., & Pahl, J. J. (1988). Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *The American Journal of Psychiatry, 145*(12), 1560–1563.

Beauchaine, T. P. (2009). Role of biomarkers and endophenotypes in prevention and treatment of psychopathological disorders. *Biomarkers in Medicine, 3*, 1–3.

Beauchaine, T. P., & Constantino, J. N. (2017). Redefining the endophenotype concept to accommodate transdiagnostic vulnerabilities and etiological complexity. *Biomarkers in Medicine, 11*(9), 769–780.

Bebbington, P. E. (1998). Epidemiology of obsessive-compulsive disorder. *British Journal of Psychiatry, Suppl*(35), 2–6.

Becker, W., & Fuchs, A. F. (1985). Prediction in the oculomotor system: smooth pursuit during transient disappearance of a visual target. *Experimental Brain Research, 57*(3), 562–575.

Berg, W. K., Byrd, D. L., McNamara, J. P., & Case, K. (2010). Deconstructing the tower: Parameters and predictors of problem difficulty on the Tower of London task. *Brain and Cognition, 72*(3), 472–482.

Bernstein, D. P., Ahluvalia, T., Pogge, D., & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(3), 340–348.

Beucke, J. C., Sepulcre, J., Eldaief, M. C., Sebold, M., Kathmann, N., & Kaufmann, C. (2014). Default mode network subsystem alterations in obsessive-compulsive disorder. *The British Journal of Psychiatry*, *205*(5), 376–382.

Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., ... & Kathmann, N. (2013). Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA Psychiatry, 70*(6), 619–629.

Bey, K., Lennertz, L., Markett, S., Petrovsky, N., Gallinat, J., Gründer, G., ... & Wagner, M. (2016). Replication of the association between CHRNA4 rs1044396 and harm avoidance in a large population-based sample. European *Neuropsychopharmacology, 26*(1), 150–155.

Bilder, R. M. (2008). Phenomics: building scaffolds for biological hypotheses in the post-genomic era. *Biological Psychiatry, 63*(5), 439–440.

Blangero, J., Williams, J. T., & Almasy, L. (2003). Novel family-based approaches to genetic risk in thrombosis. *Journal of Thrombosis and Haemostasis, 1(*7), 1391–1397.

Bleich, S., Havemann-Reinecke, U., & Kornhuber, J. (2002). *Fagerström-Test für Nikotinabhängigkeit (FTNA).* Göttingen: Beltz Test GmbH.

Bloch, M. H., Landeros-Weisenberger, A., Rosario, M. C., Pittenger, C., & Leckman, J. F. (2008). Meta-analysis of the symptom structure of obsessive-compulsive disorder. *American Journal of Psychiatry,165*(12),1532–1542.

Boedhoe, P. S., Schmaal, L., Abe, Y., Alonso, P., Ameis, S. H., Anticevic, A., ... & ENIGMA OCD Working Group (2017). Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group. *American Journal of Psychiatry*.

Boedhoe, P. S., Schmaal, L., Abe, Y., Ameis, S. H., Arnold, P. D., Batistuzzo, M. C., ... & van den Heuvel, O. A. (2016). Distinct subcortical volume alterations in pediatric and adult OCD: a worldwide meta-and mega-analysis. *American Journal of Psychiatry, 174*(1), 60–69.

Brainstorm Consortium, Anttila, V., Bulik-Sullivan, B., Walters, R. K., Finucane, H. K., Bras, J., ... & Neale, B. (2018). Analysis of shared heritability in common disorders of the brain. *Science, 360*(6395), eaap8757.

Brakoulias, V., Starcevic, V., Berle, D., Milicevic, D., Hannan, A., Viswasam, K., & Mann, K. (2014). The clinical characteristics of obsessive compulsive disorder associated with high levels of schizotypy. *Australian & New Zealand Journal of Psychiatry, 48*(9), 852–860.

Breiter, H. C., Rauch, S. L., Kwong, K. K., Baker, J. R., Weisskoff, R. M., Kennedy, D. N., ... & Rosen, B. R. (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Archives of General Psychiatry, 53*(7), 595–606.

Browne, H. A., Gair, S. L., Scharf, J. M., & Grice, D. E. (2014). Genetics of obsessive-compulsive disorder and related disorders. *Psychiatric Clinics of North America, 37*(3), 319–335.

Calkins, M. E., Curtis, C. E., & Grove, W. M. (2004). Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. *Schizophrenia Bulletin, 30*(2), 317–325.

Calvo, R., Lázaro, L., Castro-Fornieles, J., Font, E., Moreno, E., & Toro, J. (2009). Obsessive-compulsive personality disorder traits and personality dimensions in parents of children with obsessive-compulsive disorder. E*uropean Psychiatry, 24*(3), 201–206.

Cameron, I. G., Pari, G., Alahyane, N., Brien, D. C., Coe, B. C., Stroman, P. W., & Munoz, D. P. (2012). Impaired executive function signals in motor brain regions in Parkinson's disease. *NeuroImage, 60*(2), 1156–1170.

Cannon, T. D., & Keller, M. C. (2006). Endophenotypes in the genetic analyses of mental disorders. *Annual Review of Clinical Psychology, 2*, 267–290.

Cavallini, M. C., Di Bella, D., Siliprandi, F., Malchiodi, F., & Bellodi, L. (2002). Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. *American Journal of Medical Genetics Part A, 114*(3), 347–353.

Cavedini, P., Zorzi, C., Piccinni, M., Cavallini, M. C., & Bellodi, L. (2010). Executive dysfunctions in obsessive-compulsive patients and unaffected relatives: searching for a new intermediate phenotype. *Biological Psychiatry, 67*(12), 1178–1184.

Chamberlain, S. R., & Menzies, L. (2009). Endophenotypes of obsessive–compulsive disorder: rationale, evidence and future potential. *Expert Review of Neurotherapeutics, 9*(8), 1133–1146.

Chamberlain, S. R., Blackwell, A. D., Fineberg, N. A., Robbins, T. W., & Sahakian, B. J. (2005). The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience & Biobehavioral Reviews, 29*(3), 399–419.

Chamberlain, S. R., Fineberg, N. A., Menzies, L. A., Blackwell, A. D., Bullmore, E. T., Chir, B., ... & Sahakian, B. J. (2007). Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *American Journal of Psychiatry, 164*(2), 335–338.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants: A proposal. *Archives of General Psychiatry, 44*(6), 573–588.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry, 50*(12), 975–990.

Coe, B. C., & Munoz, D. P. (2017). Mechanisms of saccade suppression revealed in the anti-saccade task. *Philosophical Transactions of the Royal Society B*, *372*(1718), 20160192.

Coe, B., Tomihara, K., Matsuzawa, M., & Hikosaka, O. (2002). Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. *Journal of Neuroscience, 22*(12), 5081–5090.

Coles, M. E., Frost, R. O., Heimberg, R. G., & Rhéaume, J. (2003). “Not just right experiences”: perfectionism, obsessive–compulsive features and general psychopathology. *Behaviour Research and Therapy, 41*(6), 681–700.

Costa, P. T., & MacCrae, R. R. (1992). *Revised NEO personality inventory (NEO PI-R) and NEO five-factor inventory (NEO-FFI): Professional manual*. Lutz, FL: Psychological Assessment Resources, Inc.

Cullen, B., Samuels, J., Grados, M., Landa, R., Bienvenu, O. J., Liang, K. Y., ... & Nestadt, G. (2008). Social and communication difficulties and obsessive-compulsive disorder. *Psychopathology, 41*(3), 194–200.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine, 11*(1), 126.

Cutsuridis, V. (2017). Behavioural and computational varieties of response inhibition in eye movements. *Philosophical Transactions of the Royal Society B, 372*(1718), 20160196.

Damilou, A., Apostolakis, S., Thrapsanioti, E., Theleritis, C., & Smyrnis, N. (2016). Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. *Psychophysiology, 53*(6), 796–805.

Davis, L. K., Yu, D., Keenan, C. L., Gamazon, E. R., Konkashbaev, A. I., Derks, E. M., ... & Scharf, J. M. (2013). Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture. *PLoS Genetics, 9*(10), e1003864.

Del Casale, A., Kotzalidis, G. D., Rapinesi, C., Serata, D., Ambrosi, E., Simonetti, A., ... & Girardi, P. (2011). Functional neuroimaging in obsessive-compulsive disorder. *Neuropsychobiology, 64*(2), 61–85.

Delorme, R., Goussé, V., Roy, I., Trandafir, A., Mathieu, F., Mouren-Siméoni, M. C., ... & Leboyer, M. (2007). Shared executive dysfunctions in unaffected relatives of patients with autism and obsessive-compulsive disorder. *European Psychiatry, 22*(1), 32–38.

den Braber, A., Bohlken, M. M., Brouwer, R. M., van't Ent, D., Kanai, R., Kahn, R. S., ... & Boomsma, D. I. (2013). Heritability of subcortical brain measures: a perspective for future genome-wide association studies. *NeuroImage, 83*, 98–102.

Dias, E. C., & Segraves, M. A. (1999). Muscimol-induced inactivation of monkey frontal eye field: effects on visually and memory-guided saccades. *Journal of Neurophysiology, 81*(5), 2191–2214.

Ding, J., Powell, D., & Jiang, Y. (2009). Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. *Human Brain Mapping, 30*(11), 3541–3552.

Duchowski, A. T. (2007). *Eye tracking methodology: Theory and practice*. (2nd ed.). London: Springer.

Ecker, W., Gönner, S., & Wilm, K. (2011). The measurement of motivational dimensions of OCD: incompleteness and harm avoidance. *Psychotherapie, Psychosomatik, Medizinische Psychologie, 61*(2), 62–69.

Ericson, M., Tuvblad, C., Raine, A., Young-Wolff, K., & Baker, L. A. (2011). Heritability and longitudinal stability of schizotypal traits during adolescence. *Behavior Genetics, 41*(4), 499–511.

Ettelt, S., Grabe, H. J., Ruhrmann, S., Buhtz, F., Hochrein, A., Kraft, S., ... & Wagner, M. (2008). Harm avoidance in subjects with obsessive-compulsive disorder and their families. *Journal of Affective Disorders, 107*(1), 265–269.

Ettinger, U., Mohr, C., Gooding, D. C., Cohen, A. S., Rapp, A., Haenschel, C., & Park, S. (2015). Cognition and brain function in schizotypy: a selective review. *Schizophrenia Bulletin, 41*(suppl_2), S417–S426.

Ettinger, U., Williams, S. C., Meisenzahl, E. M., Möller, H. J., Kumari, V., & Koutsouleris, N. (2012). Association between brain structure and psychometric schizotypy in healthy individuals. *The World Journal of Biological Psychiatry, 13*(7), 544–549.

Fagerström, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors, 3*(3-4), 235–241.

Fan, S., van den Heuvel, O. A., Cath, D. C., van der Werf, Y. D., de Wit, S. J., de Vries, F. E., ... & Pouwels, P. J. (2016). Mild white matter changes in un-medicated obsessive-compulsive disorder patients and their unaffected siblings. *Frontiers in Neuroscience, 9*, 495.

Faravelli, C., Sauro, C. L., Godini, L., Lelli, L., Benni, L., Pietrini, F., ... & Ricca, V. (2012). Childhood stressful events, HPA axis and anxiety disorders. *World Journal of Psychiatry, 2*(1), 13–25.

Farber, R. H., Clementz, B. A., & Swerdlow, N. R. (1997). Characteristics of open- and closed-loop smooth pursuit responses among obsessive-compulsive disorder, schizophrenia, and nonpsychiatric individuals. *Psychophysiology, 34*(2), 157–162.

Fineberg, N. A., Apergis-Schoute, A. M., Vaghi, M. M., Banca, P., Gillan, C. M., Voon, V., ... & Bullmore, E. T. (2017). Mapping Compulsivity in the DSM-5 Obsessive Compulsive and Related Disorders: Cognitive Domains, Neural Circuitry, and Treatment. *International Journal of Neuropsychopharmacology, 21*(1), 42–58.

Fineberg, N. A., Brown, A., Reghunandanan, S., & Pampaloni, I. (2012). Evidence-based pharmacotherapy of obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology, 15*(8), 1173–1191.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *User's guide for the Structured Clinical Interview for DSM-IV axis I Disorders SCID-I: clinician version*. Arlington, VA: American Psychiatric Association Publishing.

First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B., Davies, M., Borus, J., ... & Rounsaville, B. (1995). The structured clinical interview for DSM-III-R personality disorders (SCID-II). Part II: Multi-site test-retest reliability study. *Journal of Personality Disorders, 9*(2), 92–104.

Fischer, B., & Ramsperger, E. (1984). Human express saccades: extremely short reaction times of goal directed eye movements. *Experimental Brain Research, 57*(1), 191–195.

Flint, J., & Munafò, M. R. (2007). The endophenotype concept in psychiatric genetics. *Psychological Medicine, 37*(2), 163–180.

Flint, J., Valdar, W., Shifman, S., & Mott, R. (2005). Strategies for mapping and cloning quantitative trait genes in rodents. *Nature Reviews Genetics, 6*(4), 271–286.

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: development and validation of a short version. *Psychological Assessment, 14*(4), 485–496.

Franklin, M. E., & Foa, E. B. Treatment of obsessive compulsive disorder. *Annual Review of Clinical Psychology, 7*, 229–243.

Fu, Y., Ma, Z., Hamilton, C., Liang, Z., Hou, X., Ma, X., ... & Zhang, N. (2015). Genetic influences on resting-state functional networks: A twin study. *Human Brain Mapping, 36*(10), 3959–3972.

Gambini, O., Abbruzzese, M., & Scarone, S. (1993). Smooth pursuit and saccadic eye movements and Wisconsin Card Sorting Test performance in obsessive-compulsive disorder. *Psychiatry Research, 48*(3), 191–200.

Garcia, D., Lundström, S., Brändström, S., Råstam, M., Cloninger, C. R., Kerekes, N., ... & Anckarsäter, H. (2013). Temperament and Character in the Child and Adolescent Twin Study in Sweden (CATSS): comparison to the general population, and genetic structure analysis*. PLoS One, 8*(8), e70475.

Geller, D., Biederman, J., Jones, J., Park, K., Schwartz, S., Shapiro, S., & Coffey, B. (1998). Is juvenile obsessive-compulsive disorder a developmental subtype of the disorder? A review of the pediatric literature. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*(4), 420–427.

Gillan, C. M., Papmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., & de Wit, S. (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *American Journal of Psychiatry, 168*(7), 718-726.

Gillan, C. M., & Robbins, T. W. (2014). Goal-directed learning and obsessive–compulsive disorder. *Philosophical Transactions of the Royal Society B, 369*(1655), 20130475.

Gillespie, N. A., Cloninger, C. R., Heath, A. C., & Martin, N. G. (2003). The genetic and environmental relationship between Cloninger's dimensions of temperament and character. *Personality and Individual Differences, 35*(8), 1931–1946.

Glahn, D. C., Curran, J. E., Winkler, A. M., Carless, M. A., Kent, J. W., Charlesworth, J. C., ... & Blangero, J. (2012). High dimensional endophenotype ranking in the search for major depression risk genes. *Biological Psychiatry, 71*(1), 6–14.

Glahn, D. C., Knowles, E. E., McKay, D. R., Sprooten, E., Raventós, H., Blangero, J., ... & Almasy, L. (2014). Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 165*(2), 122–130.

Gönner, S., Leonhart, R., & Ecker, W. (2008). The obsessive–compulsive inventory-revised (OCI-R): validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. *Journal of Anxiety Disorders, 22*(4), 734–749.

González-Giraldo, Y., González-Reyes, R. E., Mueller, S. T., Piper, B. J., Adan, A., & Forero, D. A. (2015). Differences in planning performance, a neurocognitive endophenotype, are associated with a functional variant in PER3 gene. *Chronobiology International, 32*(5), 591–595.

Gooding, D. C., Tallent, K. A., & Matts, C. W. (2005). Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. *Journal of Abnormal Psychology, 114*(1), 170–175.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale Brown Obsessive Compulsive Scale: II. Validity. *Archives of General Psychiatry, 46*(11), 1012–1016.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645.

Göttlich, M., Krämer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. (2014). Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. *Human Brain Mapping, 35*(11), 5617–5632.

Gould, T. D., & Gottesman, I. I. (2006). Psychiatric endophenotypes and the development of valid animal models. *Genes, Brain and Behavior, 5*(2), 113–119.

Grabe, H. J., Ruhrmann, S., Ettelt, S., Buhtz, F., Hochrein, A., Schulze-Rauschenbach, S., ... & Wagner, M. (2006). Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. *American Journal of Psychiatry, 163*(11), 1986–1992.

Green, J. F., King, D. J., & Trimble, K. M. (2000). Antisaccade and smooth pursuit eye movements in healthy subjects receiving sertraline and lorazepam. *Journal of Psychopharmacology, 14(*1), 30–36.

Greenwood, T. A., Braff, D. L., Light, G. A., Cadenhead, K. S., Calkins, M. E., Dobie, D. J., ... & Schork, N. J. (2007). Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Archives of General Psychiatry, 64*(11), 1242–1250.

Greenwood, T. A., Lazzeroni, L. C., Murray, S. S., Cadenhead, K. S., Calkins, M. E., Dobie, D. J., ... & Braff, D. L. (2011). Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *American Journal of Psychiatry, 168*(9), 930–946.

Greenwood, T. A., Light, G. A., Swerdlow, N. R., Radant, A. D., & Braff, D. L. (2012). Association analysis of 94 candidate genes and schizophrenia-related endophenotypes. *PloS One, 7*(1), e29630.

Guitton, D., Buchtel, H. A., & Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research, 58*(3), 455–472.

Gürsel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neuroscience & Biobehavioral Reviews*.

Haber, S. N., & Heilbronner, S. R. (2013). Translational research in OCD: circuitry and mechanisms. *Neuropsychopharmacology, 38*(1), 252–253.

Hakvoort Schwerdtfeger, R. M., Alahyane, N., Brien, D. C., Coe, B. C., Stroman, P. W., & Munoz, D. P. (2013). Preparatory neural networks are impaired in adults with attention-deficit/hyperactivity disorder during the antisaccade task. *NeuroImage: Clinical, 2*, 63–78.

Hand, I., & Büttner-Westphal, H. (1991). Die Yale-Brown Obsessive Compulsive Scale (Y-BOCS): Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen. *Verhaltenstherapie, 1*(3), 223–225.

Hanna, G. L., Veenstra-VanderWeele, J., Cox, N. J., Boehnke, M., Himle, J. A., Curtis, G. C., ... & Cook, E. H. (2002). Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *American Journal of Medical Genetics Part A, 114*(5), 541–552.

Hanna, G. L., Veenstra-VanderWeele, J., Cox, N. J., Van Etten, M., Fischer, D. J., Himle, J. A., ... & Cook, E. H. (2007). Evidence for a susceptibility locus on chromosome 10p15 in early-onset obsessive-compulsive disorder. *Biological Psychiatry, 62*(8), 856–862.

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., ... & Cardoner, N. (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of General Psychiatry, 66*(11), 1189–1200.

Hasler, G., Drevets, W. C., Gould, T. D., Gottesman, I. I., & Manji, H. K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biological Psychiatry, 60*(2), 93–105.

Hasler, G., Kazuba, D., & Murphy, D. L. (2006). Factor analysis of obsessive–compulsive disorder YBOCS-SC symptoms and association with 5-HTTLPR SERT polymorphism. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 141*(4), 403–408.

Hasler, G., LaSalle-Ricci, V. H., Ronquillo, J. G., Crawley, S. A., Cochran, L. W., Kazuba, D., ... & Murphy, D. L. (2005). Obsessive–compulsive disorder symptom dimensions show specific relationships to psychiatric comorbidity. *Psychiatry Research, 135*(2), 121–132.

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II).* Frankfurt: Harcourt Test Services.

Hemmings, S. M. J., Lochner, C., van der Merwe, L., Cath, D. C., Seedat, S., & Stein, D. J. (2013). BDNF Val66Met modifies the risk of childhood trauma on obsessive-compulsive disorder. *Journal of Psychiatric Research, 47*(12), 1857–1863.

Hibar, D. P., Stein, J. L., Renteria, M. E., Arias-Vasquez, A., Desrivières, S., Jahanshad, N., ... & Medland, S. E. (2015). Common genetic variants influence human subcortical brain structures. *Nature, 520*(7546), 224–229.

Hong, L. E., Mitchell, B. D., Avila, M. T., Adami, H., McMahon, R. P., & Thaker, G. K. (2006). Familial aggregation of eye-tracking endophenotypes in families of schizophrenic patients. *Archives of General Psychiatry, 63*(3), 259–264.

Hou, J. M., Zhao, M., Zhang, W., Song, L. H., Wu, W. J., Wang, J., ... & Li, H. T. (2014). Resting-state functional connectivity abnormalities in patients with obsessive–compulsive disorder and their healthy first-degree relatives. *Journal of Psychiatry & Neuroscience, 39*(5), 304–311.

Hu, X., Du, M., Chen, L., Li, L., Zhou, M., Zhang, L., ... & Gong, Q. (2017). Meta-analytic investigations of common and distinct grey matter alterations in youths and adults with obsessive-compulsive disorder. *Neuroscience & Biobehavioral Reviews, 78*, 91–103.

Hutton, S. B. (2008). Cognitive control of saccadic eye movements. *Brain and Cognition, 68*(3), 327–340.

Iacono, W. G. (2018). Endophenotypes in psychiatric disease: prospects and challenges. *Genome Medicine, 10(*1), 11.

Iacono, W. G., Malone, S. M., & Vrieze, S. I. (2017). Endophenotype best practices. *International Journal of Psychophysiology, 111*, 115–144.

Iacono, W. G., Vaidyanathan, U., Vrieze, S. I., & Malone, S. M. (2014). Knowns and unknowns for psychophysiological endophenotypes: Integration and response to commentaries. *Psychophysiology, 51*(12), 1339–1347.

Iervolino, A. C., Rijsdijk, F. V., Cherkas, L., Fullana, M. A., & Mataix-Cols, D. (2011). A multivariate twin study of obsessive-compulsive symptom dimensions. *Archives of General Psychiatry, 68*(6), 637–644.

Iervolino, A. C., Rijsdijk, F. V., Cherkas, L., Fullana, M. A., & Mataix-Cols, D. (2011). A multivariate twin study of obsessive-compulsive symptom dimensions. *Archives of General Psychiatry, 68*(6), 637–644.

International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2017). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Molecular Psychiatry*, *23*(5), 1181–1188.

Ioannidis, J. P. (2008). Why most discovered true associations are inflated. *Epidemiology, 19*(5), 640–648.

Jaafari, N., Rigalleau, F., Rachid, F., Delamillieure, P., Millet, B., Olié, J.-P. P., … Vibert, N. (2011). A critical review of the contribution of eye movement recordings to the neuropsychology of obsessive compulsive disorder. *Acta Psychiatrica Scandinavica, 124*(2), 87–101.

Johnston, K., Koval, M. J., Lomber, S. G., & Everling, S. (2013). Macaque dorsolateral prefrontal cortex does not suppress saccade-related activity in the superior colliculus. *Cerebral Cortex, 24*(5), 1373–1388.

Josefsson, K., Jokela, M., Cloninger, C. R., Hintsanen, M., Salo, J., Hintsa, T., ... & Keltikangas-Järvinen, L. (2013). Maturity and change in personality: developmental trends of temperament and character in adulthood. *Development and Psychopathology, 25*(3), 713–727.

Kaller, C. P., Rahm, B., Köstering, L., & Unterrainer, J. M. (2011). Reviewing the impact of problem structure on planning: A software tool for analyzing tower tasks. *Behavioural Brain Research, 216*(1), 1–8.

Kaller, C. P., Unterrainer, J. M., & Stahl, C. (2012). Assessing planning ability with the Tower of London task: Psychometric properties of a structurally balanced problem set. *Psychological Assessment, 24*(1), 46–53.

Kaller, C. P., Unterrainer, J. M., Rahm, B., & Halsband, U. (2004). The impact of problem structure on planning: Insights from the Tower of London task. *Cognitive Brain Research, 20*(3), 462–472.

Katerberg, H., Delucchi, K. L., Stewart, S. E., Lochner, C., Denys, D. A., Stack, D. E., ... & Cath, D. C.. (2010). Symptom dimensions in OCD: item-level factor analysis and heritability estimates. *Behavior Genetics, 40*(4), 505–517.

Katsanis, J., Taylor, J., Iacono, W. G., & Hammer, M. A. (2000). Heritability of different measures of smooth pursuit eye tracking dysfunction: a study of normal twins. *Psychophysiology, 37*(6), 724–730.

Kattoulas, E., Smyrnis, N., Stefanis, N. C., Avramopoulos, D., Stefanis, C. N., & Evdokimidis, I. (2011). Predictive smooth eye pursuit in a population of young men: I. Effects of age, IQ, oculomotor and cognitive tasks. *Experimental Brain Research, 215*(3–4), 207–218.

Kattoulas, E., Stefanis, N. C., Avramopoulos, D., Stefanis, C. N., Evdokimidis, I., & Smyrnis, N. (2012). Schizophrenia-related RGS4 gene variations specifically disrupt prefrontal control of saccadic eye movements. *Psychological Medicine, 42*(4), 757-767.

Keller, M. C., Coventry, W. L., Heath, A. C., & Martin, N. G. (2005). Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior Genetics, 35*(6), 707.

Kendler, K. S., & Hewitt, J. (1992). The structure of self-report schizotypy in twins. *Journal of Personality Disorders, 6*(1), 1–17.

Kendler, K. S., McGuire, M., Gruenberg, A. M., & Walsh, D. (1995). Schizotypal symptoms and signs in the Roscommon Family Study: Their factor structure and familial relationship with psychotic and affective disorders. *Archives of General Psychiatry, 52*(4), 296–303.

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E. V. A., ... & Walters, E. E. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychological Medicine, 35*(2), 245–256.

Kim, S. J., Kang, J. I., & Kim, C. H. (2009). Temperament and character in subjects with obsessive-compulsive disorder. *Comprehensive Psychiatry, 50*(6), 567–572.

Kloft, L., Kischkel, E., Kathmann, N., & Reuter, B. (2011). Evidence for a deficit in volitional action generation in patients with obsessive-compulsive disorder. *Psychophysiology, 48*(6), 755–761.

Kloft, L., Reuter, B., Riesel, A., & Kathmann, N. (2013). Impaired volitional saccade control: first evidence for a new candidate endophenotype in obsessive–compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience, 263*(3), 215–222.

Koch, K., Wagner, G., Schachtzabel, C., Schultz, C. C., Straube, T., Güllmar, D., ... & Schlösser, R. G. (2012). White matter structure and symptom dimensions in obsessive–compulsive disorder. *Journal of Psychiatric Research, 46*(2), 264–270.

Köstering, L., Schmidt, C. S., Egger, K., Amtage, F., Peter, J., Klöppel, S., ... & Kaller, C. P. (2015). Assessment of planning performance in clinical samples: Reliability and validity of the Tower of London task (TOL-F). *Neuropsychologia, 75*, 646–655.

Krieghoff, V., Waszak, F., Prinz, W., & Brass, M. (2011). Neural and behavioral correlates of intentional actions. *Neuropsychologia, 49*(5), 767–776.

Lázaro, L., Ortiz, A. G., Calvo, A., Ortiz, A. E., Moreno, E., Morer, A., ... & Bargallo, N. (2014). White matter structural alterations in pediatric obsessive–compulsive disorder: Relation to symptom dimensions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 54*, 249–258.

Laux, L., & Spielberger, C. D. (2001). Das State-Trait-Angstinventar: STAI. Göttingen: Beltz Test.

Leckman, J. F., Pauls, D. L., Zhang, H., Rosario-Campos, M. C., Katsovich, L., Kidd, K. K., ... & Tourette Syndrome Assocation International Consortium for Genetics. (2003). Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 116*(1), 60–68.

Leckman, J. F., Riddle, M. A., Hardin, M. T., Ort, S. I., Swartz, K. L., Stevenson, J. O. H. N., & Cohen, D. J. (1989). The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *Journal of the American Academy of Child & Adolescent Psychiatry, 28*(4), 566–573.

Leigh, J. R., & Zee, D. S. (2015). *The neurology of eye movements*. Oxford: Oxford University Press.

Lencer, R., & Trillenberg, P. (2008). Neurophysiology and neuroanatomy of smooth pursuit in humans. *Brain and Cognition, 68*(3), 219–228.

Lencer, R., Mills, L. J., Alliey-Rodriguez, N., Shafee, R., Lee, A. M., Reilly, J. L., ... & Bishop, J. R. (2017). Genome-wide association studies of smooth pursuit and antisaccade eye movements in psychotic disorders: findings from the B-SNIP study. *Translational Psychiatry, 7*(10), e1249.

Lencer, R., Nagel, M., Sprenger, A., Zapf, S., Erdmann, C., Heide, W., & Binkofski, F. (2004). Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *European Journal of Neuroscience, 19*(5), 1430–1436.

Lencer, R., Trillenberg, P., Trillenberg-Krecker, K., Junghanns, K., Kordon, A., Brooks, A., … Arolt, V. (2004). Smooth pursuit deficits in schizophrenia, affective disorder and obsessive-compulsive disorder. *Psychological Medicine, 34*(3), 451–460.

Lennertz, L., Rampacher, F., Vogeley, A., Schulze-Rauschenbach, S., Pukrop, R., Ruhrmann, S., ... & Wagner, M. (2012). Antisaccade performance in patients with obsessive–compulsive disorder and unaffected relatives: further evidence for impaired response inhibition as a candidate endophenotype. *European Archives of Psychiatry and Clinical Neuroscience, 262*(7), 625–634.

Lenzenweger, M. F. (2010). *Schizotypy and Schizophrenia: The View from Experimental Psychopathology*. New York, NY: Guilford Press.

Lewis, A (1936). Problems of obsessional illness: (section of psychiatry). *Proceedings of the Royal Society of Medicine, 29*, 325–336.

Lilienfeld, S. O. (2014). The Research Domain Criteria (RDoC): An analysis of methodological and conceptual challenges. *Behaviour Research and Therapy, 62*, 129–139.

Lin, C. C., Su, C. H., Kuo, P. H., Hsiao, C. K., Soong, W. T., & Chen, W. J. (2007). Genetic and environmental influences on schizotypy among adolescents in Taiwan: a multivariate twin/sibling analysis. *Behavior Genetics, 37*(2), 334–344.

Linney, Y. M., Murray, R. M., Peters, E. R., MacDonald, A. M., Rijsdijk, F., & Sham, P. C. (2003). A quantitative genetic analysis of schizotypal personality traits. *Psychological Medicine, 33*(5), 803–816.

Liu, J., Pei, Y., Papasian, C. J., & Deng, H. W. (2009). Bivariate association analyses for the mixture of continuous and binary traits with the use of extended generalized estimating equations. *Genetic Epidemiology, 33*(3), 217–227.

Liversedge, S., Gilchrist, I., & Everling, S. (2011). *The Oxford handbook of eye movements*. Oxford: Oxford University Press.

Lochner, C., du Toit, P. L., Zungu-Dirwayi, N., Marais, A., van Kradenburg, J., Seedat, S., ... & Stein, D. J. (2002). Childhood trauma in obsessive-compulsive disorder, trichotillomania, and controls. *Depression and Anxiety, 15*(2), 66–68.

Lovinger, D. M. (2010). Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. *Neuropharmacology, 58*(7), 951–961.

Lyoo, I. K., Yoon, T., Kang, D. H., & Kwon, J. S. (2003). Patterns of changes in temperament and character inventory scales in subjects with obsessive–compulsive disorder following a 4-month treatment. *Acta Psychiatrica Scandinavica, 107*(4), 298–304.

Malone, S. M., & Iacono, W. G. (2002). Error rate on the antisaccade task: heritability and developmental change in performance among preadolescent and late-adolescent female twin youth. *Psychophysiology, 39*(5), 664–673.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., ... & Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature, 461*(7265), 747–753.

Markett, S., Weber, B., Voigt, G., Montag, C., Felten, A., Elger, C., & Reuter, M. (2013). Intrinsic connectivity networks and personality: the temperament dimension harm avoidance moderates functional connectivity in the resting brain. *Neuroscience, 240*, 98–105.

Maruff, P., Purcell, R., Tyler, P., Pantelis, C., & Currie, J. (1999). Abnormalities of internally generated saccades in obsessive–compulsive disorder. *Psychological Medicine, 29*(6), 1377–1385.

Mataix-Cols, D., Boman, M., Monzani, B., Rück, C., Serlachius, E., Långström, N., & Lichtenstein, P. (2013). Population-based, multigenerational family clustering study of obsessive-compulsive disorder. *JAMA Psychiatry, 70*(7), 709–717.

Mataix-Cols, D., do Rosario-Campos, M. C., & Leckman, J. F. (2005). A multidimensional model of obsessive-compulsive disorder. *American Journal of Psychiatry, 162*(2), 228–238.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M. J., Speckens, A., & Phillips, M. L. (2004). Distinct neural correlates of washing, checking, and hoarding symptomdimensions in obsessive-compulsive disorder. *Archives of General Psychiatry, 61*(6), 564–576.

Mathews, C. A., Badner, J. A., Andresen, J. M., Sheppard, B., Himle, J. A., Grant, J. E., ... & Hanna, G. L. (2012). Genome-wide linkage analysis of obsessive-

compulsive disorder implicates chromosome 1p36. *Biological Psychiatry, 72*(8), 629–636.

Mattheisen, M., Samuels, J. F., Wang, Y., Greenberg, B. D., Fyer, A. J., McCracken, J. T., ... & Nestadt, G. (2015). Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. *Molecular Psychiatry, 20*(3), 337–344.

Maunsell, J. H., & Newsome, W. T. (1987). Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience, 10*(1), 363–401.

McCarthy, M. J. (2011). The eyes are the window to the brain: reviewing oculomotor abnormalities in obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica, 124*(2), 85–86.

McDowell, J. E., & Clementz, B. A. (1997). The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. *Experimental Brain Research, 115*(2), 333–344.

McGregor, N. W., Hemmings, S. M. J., Erdman, L., Calmarza-Font, I., Stein, D. J., & Lochner, C. (2016). Modification of the association between early adversity and obsessive-compulsive disorder by polymorphisms in the MAOA, MAOB and COMT genes. *Psychiatry Research, 246*, 527–532.

McKinlay, A., Kaller, C. P., Grace, R. C., Dalrymple-Alford, J. C., Anderson, T. J., Fink, J., & Roger, D. (2008). Planning in Parkinson's disease: A matter of problem structure?. *Neuropsychologia, 46*(1), 384–389.

Melo-Felippe, F. B., de Salles Andrade, J. B., Giori, I. G., Vieira-Fonseca, T., Fontenelle, L. F., & Kohlrausch, F. B. (2016). Catechol-O-Methyltransferase Gene Polymorphisms in Specific Obsessive–Compulsive Disorder Patients' Subgroups. *Journal of Molecular Neuroscience, 58*(1), 129–136.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences, 15*(10), 483–506.

Menzies, L., Achard, S., Chamberlain, S. R., Fineberg, N., Chen, C. H., Del Campo, N., ...Bullmore, E. (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain, 130*(12), 3223–3236.

Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-

striatal model revisited. *Neuroscience & Biobehavioral Reviews, 32*(3), 525–549.

Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology, 110*(1), 40–48.

Miller, G. A., & Rockstroh, B. (2013). Endophenotypes in psychopathology research: where do we stand?. *Annual Review of Clinical Psychology, 9*, 177–213.

Moates, A. F., Ivleva, E. I., O'Neill, H. B., Krishna, N., Cullum, C. M., Thaker, G. K., & Tamminga, C. A. (2012). Predictive pursuit association with deficits in working memory in psychosis. *Biological Psychiatry, 72*(9), 752–757.

Montgomery, S. A., & Asberg, M. A. R. I. E. (1979). A new depression scale designed to be sensitive to change. The British Journal of Psychiatry, 134(4), 382–389.

Mortensen, P. B., Pedersen, C. B., Westergaard, T., Wohlfahrt, J., Ewald, H., Mors, O., ... & Melbye, M. (1999). Effects of family history and place and season of birth on the risk of schizophrenia. *New England Journal of Medicine, 340*(8), 603–608.

Munoz, D. P., & Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5*(3), 218–228.

Munoz, D. P., & Fecteau, J. H. (2002). Vying for dominance: dynamic interactions control visual fixation and saccadic initiation in the superior colliculus. *Progress in Brain Research,140*, 3–19.

Munoz, D. P., & Wurtz, R. H. (1992). Role of the rostral superior colliculus in active visual fixation and execution of express saccades. *Journal of Neurophysiology, 67*(4), 1000–1002.

Murayama, K., Nakao, T., Sanematsu, H., Okada, K., Yoshiura, T., Tomita, M., ... & Kanba, S. (2013). Differential neural network of checking versus washing symptoms in obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 40*, 160–166.

Murray, C. J. & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *The Lancet, 349*(9063), 1436–1442

Nagel, M., Sprenger, A., Hohagen, F., Binkofski, F., & Lencer, R. (2008). Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *NeuroImage, 41*(2), 483–492.

Nakao, T., Okada, K., & Kanba, S. (2014). Neurobiological model of obsessive–compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. *Psychiatry and Clinical Neurosciences, 68*(8), 587–605.

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O. J., Liang, K. Y., LaBuda, M., ... & Hoehn-Saric, R. (2000). A family study of obsessive-compulsive disorder. *Archives of General Psychiatry, 57*(4), 358–363.

Neumann, N. U., & Schulte, R. M. (1989). *Montgomery and Asberg Depression Rating Scale. Deutsche Fassung*. Erlangen: Perimed Fachbuch Verlagsgesellschaft.

Noh, H. J., Tang, R., Flannick, J., O'Dushlaine, C., Swofford, R., Howrigan, D., ... & Lindblad-Toh, K.. (2017). Integrating evolutionary and regulatory information with a multispecies approach implicates genes and pathways in obsessive-compulsive disorder. *Nature Communications, 8*(1), 774.

O'Reilly, P. F., Hoggart, C. J., Pomyen, Y., Calboli, F. C., Elliott, P., Jarvelin, M. R., & Coin, L. J. (2012). MultiPhen: joint model of multiple phenotypes can increase discovery in GWAS. *PloS One, 7*(5), e34861.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Paré, M., & Wurtz, R. H. (2001). Progression in neuronal processing for saccadic eye movements from parietal cortex area lip to superior colliculus. *Journal of Neurophysiology, 85*(6), 2545–2562.

Pauls, D. L., Abramovitch, A., Rauch, S. L., & Geller, D. A. (2014). Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nature Reviews Neuroscience, 15*(6), 410–424.

Peng, Z. W., Xu, T., He, Q. H., Shi, C. Z., Wei, Z., Miao, G. D., ... & Chan, R. C. (2014). Default network connectivity as a vulnerability marker for obsessive compulsive disorder. *Psychological Medicine, 44*(7), 1475–1484.

Peng, Z., Li, G., Shi, F., Shi, C., Yang, Q., Chan, R. C., & Shen, D. (2015). Cortical asymmetries in unaffected siblings of patients with obsessive–compulsive disorder. *Psychiatry Research: Neuroimaging, 234*(3), 346–351.

Peng, Z., Shi, F., Shi, C., Miao, G., Yang, Q., Gao, W., ... & Shen, D. (2014). Structural and diffusion property alterations in unaffected siblings of patients with obsessive-compulsive disorder. *PloS One, 9(*1), e85663.

Peng, Z., Shi, F., Shi, C., Yang, Q., Chan, R. C., & Shen, D. (2014). Disrupted cortical network as a vulnerability marker for obsessive–compulsive disorder. *Brain Structure and Function, 219*(5), 1801–1812.

Pinhal, C. M., van den Boom, B. J., Santana-Kragelund, F., Fellinger, L., Bech, P., Hamelink, R., ... & Denys, D. (2018). Differential effects of deep-brain stimulation of the internal capsule and the striatum on excessive grooming in Sapap3 mutant mice. *Biological Psychiatry*.

Piras, F., Piras, F., Chiapponi, C., Girardi, P., Caltagirone, C., & Spalletta, G. (2015). Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex, 62*, 89–108.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annual Review of. Clinical Psychology, 2*, 291–326.

Rajender, G., Bhatia, M. S., Kanwal, K., Malhotra, S., Singh, T. B., & Chaudhary, D. (2011). Study of neurocognitive endophenotypes in drug-naïve obsessive–compulsive disorder patients, their first-degree relatives and healthy controls. *Acta Psychiatrica Scandinavica, 124*(2), 152–161.

Rasmussen, S. A., & Eisen, J. L. (1990). Epidemiology of obsessive compulsive disorder. *The Journal of Clinical Psychiatry, 51*(2, Suppl), 10–13.

Rector, N. A., Cassin, S. E., Richter, M. A., & Burroughs, E. (2009). Obsessive beliefs in first-degree relatives of patients with OCD: a test of the cognitive vulnerability model. *Journal of Anxiety Disorders, 23*(1), 145–149.

Richter, J., Eisemann, M., & Richter, G. (2000). German version of the temperament and character inventory. *Zeitschrift für Klinische Psychologie - Forschung und Praxis, 29*(2), 117–126.

Richter, M. A., Summerfeldt, L. J., Joffe, R. T., & Swinson, R. P. (1996). The Tridimensional Personality Questionnaire in obsessive-compulsive disorder. *Psychiatry Research, 65*(3), 185–188.

Riesel, A., Endrass, T., Auerbach, L. A., & Kathmann, N. (2015). Overactive performance monitoring as an endophenotype for obsessive-compulsive disorder: evidence from a treatment study. *American Journal of Psychiatry, 172*(7), 665–673.

Riesel, A., Endrass, T., Kaufmann, C., & Kathmann, N. (2011). Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive

disorder: evidence from unaffected first-degree relatives. *American Journal of Psychiatry, 168*(3), 317–324.

Robbins, T. W., Gillan, C. M., Smith, D. G., de Wit, S., & Ersche, K. D. (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in Cognitive Sciences, 16*(1), 81–91.

Rossi, A., & Daneluzzo, E. (2002). Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. *Schizophrenia Research, 54*(1), 67–75.

Rotge, J. Y., Langbour, N., Guehl, D., Bioulac, B., Jaafari, N., Allard, M., ... & Burbaud, P. (2010). Gray matter alterations in obsessive–compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology, 35*(3), 686–691.

Samuels, J., Nestadt, G., Bienvenu, O. J., Costa, P. T., Riddle, M. A., Liang, K. Y., ... & Cullen, B. A. (2000). Personality disorders and normal personality dimensions in obsessive—compulsive disorder. *The British Journal of Psychiatry, 177*(5), 457–462.

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology, 46*(5), 932–946.

Schall, J. D. (1997). Visuomotor areas of the frontal lobe. *Cerebral Cortex* 12, 527–638.

Schmidt, K. H., & Metzler, P. (1992). *WST-Wortschatztest*. Göttingen: Beltz Test GmbH.

Segalas, C., Alonso, P., Real, E., Garcia, A., Minambres, A., Labad, J., ... & Menchón, J. M. (2010). Memory and strategic processing in first-degree relatives of obsessive compulsive patients. *Psychological Medicine, 40*(12), 2001–2011.

Service, S. K., Verweij, K. J. H., Lahti, J., Congdon, E., Ekelund, J., Hintsanen, M., ... & Freimer, N. B. (2012). A genome-wide meta-analysis of association studies of Cloninger's Temperament Scales. *Translational Psychiatry, 2*(5), e116.

Shaw, P., Sharp, W., Sudre, G., Wharton, A., Greenstein, D., Raznahan, A., ... & Rapoport, J. (2015). Subcortical and cortical morphological anomalies as an endophenotype in obsessive-compulsive disorder. *Molecular Psychiatry, 20*(2), 224–231.

Shin, D. J., Jung, W. H., He, Y., Wang, J., Shim, G., Byun, M. S., ... & Kwon, J. S. (2014). The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder. *Biological Psychiatry, 75*(8), 606–614.

Shin, N. Y., Lee, T. Y., Kim, E., & Kwon, J. S. (2014). Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. *Psychological Medicine, 44*(6), 1121–1130.

Shugart, Y. Y., Samuels, J., Willour, V. L., Grados, M. A., Greenberg, B. D., Knowles, J. A., ... & Nestadt, G. (2006). Genomewide linkage scan for obsessive-compulsive disorder: evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. *Molecular Psychiatry, 11*(8), 763–770.

Siebner, H. R., Callicott, J. H., Sommer, T., & Mattay, V. S. (2009). From the genome to the phenome and back: linking genes with human brain function and structure using genetically informed neuroimaging. *Neuroscience, 164*(1), 1–6.

Simmons, J. M., & Quinn, K. J. (2014). The NIMH research domain criteria (RDoC) Project: implications for genetics research. *Mammalian Genome, 25*(1-2), 23–31.

Sinclair, B., Hansell, N. K., Blokland, G. A., Martin, N. G., Thompson, P. M., Breakspear, M., ... & McMahon, K. L. (2015). Heritability of the network architecture of intrinsic brain functional connectivity. *NeuroImage, 121*, 243–252.

Skoog, G., & Skoog, I. (1999). A 40-year follow-up of patients with obsessive-compulsive disorder. *Archives of General Psychiatry, 56*(2), 121–127.

Smyrnis, N. (2008). Metric issues in the study of eye movements in psychiatry. *Brain and Cognition, 68*(3), 341–358.

Snyder, H. R., Kaiser, R. H., Warren, S. L., & Heller, W. (2015). Obsessive-compulsive disorder is associated with broad impairments in executive function: A meta-analysis. *Clinical Psychological Science, 3*(2), 301–330.

Sobin, C., Blundell, M. L., Weiller, F., Gavigan, C., Haiman, C., & Karayiorgou, M. (2000). Evidence of a schizotypy subtype in OCD. *Journal of Psychiatric Research, 34*(1), 15–24.

Spengler, D., Trillenberg, P., Sprenger, A., Nagel, M., Kordon, A., Junghanns, K., … Lencer, R. (2006). Evidence from increased anticipation of predictive saccades

for a dysfunction of fronto-striatal circuits in obsessive-compulsive disorder. *Psychiatry Research, 143*(1), 77–88.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spinhoven, P., Elzinga, B. M., Van Hemert, A. M., de Rooij, M., & Penninx, B. W. (2016). Childhood maltreatment, maladaptive personality types and level and course of psychological distress: A six-year longitudinal study. *Journal of Affective Disorders, 191*, 100–108.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences, 105*(34), 12569–12574.

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1997). Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychological Reports, 80*(2), 443–446.

Stefanis, N. C., Trikalinos, T. A., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Ntzani, E. E., ... & Stefanis, C. N. (2007). Impact of schizophrenia candidate genes on schizotypy and cognitive endophenotypes at the population level. *Biological Psychiatry, 62*(7), 784–792.

Stefanis, N. C., Van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Hantoumi, I., & Stefanis, C. N. (2004). Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biological Psychiatry, 56*(7), 510–515.

Steinhause, H.C. (2002). *Psychische Störungen bei Kindern und Jugendlichen. Lehrbuch der Kinder- und Jugendpsychiatrie*. München: Urban & Fischer.

Stewart, S. E., Yu, D., Scharf, J. M., Neale, B. M., Fagerness, J. A., Mathews, C. A., ... & Pauls, D. L. (2013). Genome-wide association study of obsessive-compulsive disorder. *Molecular Psychiatry, 18*(7), 788–798.

Stuphorn, V., Taylor, T. L., & Schall, J. D. (2000). Performance monitoring by the supplementary eye field. *Nature, 408*(6814), 857–860.

Sullivan, P. F., Agrawal, A., Bulik, C. M., Andreassen, O. A., Børglum, A. D., Breen, G., ... & Psychiatric Genomics Consortium (2017). Psychiatric Genomics: An Update and an Agenda. *American Journal of Psychiatry, 175*(1), 15–27.

Summerfeldt, L. J., Kloosterman, P., Parker, J. D. A., Antony, M. M., & Swinson, R. P. (2001, June). Assessing and validating the obsessive-compulsive-related construct of incompleteness. In Annual Convention of the Canadian Psychological Association, Ste-Foy, Quebec. Abstract published in Canadian Psychology.

Swedo, S. E., Schapiro, M. B., Grady, C. L., Cheslow, D. L., Leonard, H. L., Kumar, A., ... & Rapoport, J. L. (1989). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of General Psychiatry, 46*(6), 518–523.

Sweeney, J. A., Palumbo, D. R., Shear, M. K., & Halper, J. P. (1992). Pursuit eye movement dysfunction in obsessive-compulsive disorder. *Psychiatry Research, 42*, 1–11.

Taylor, S. (2011). Etiology of obsessions and compulsions: a meta-analysis and narrative review of twin studies. *Clinical Psychology Review, 31*(8), 1361–1372.

Taylor, S. (2013). Molecular genetics of obsessive–compulsive disorder: a comprehensive meta-analysis of genetic association studies. *Molecular Psychiatry, 18*(7), 799–805.

Thaker, G. K., Wonodi, I., Avila, M. T., Hong, L. E., & Stine, O. C. (2004). Catechol O-methyltransferase polymorphism and eye tracking in schizophrenia: a preliminary report. *American Journal of Psychiatry, 161*(12), 2320–2322.

Tien, A. Y., Pearlson, G. D., Machlin, S. R., Bylsma, F. W., & Hoehn-Saric, R. (1992). Oculomotor performance in obsessive-compulsive disorder. *The American Journal of Psychiatry, 149*(5), 641–646.

Torres, A. R., Fontenelle, L. F., Shavitt, R. G., Ferrão, Y. A., do Rosário, M. C., Storch, E. A., & Miguel, E. C. (2016). Comorbidity variation in patients with obsessive–compulsive disorder according to symptom dimensions: results from a large multicentre clinical sample. *Journal of Affective Disorders, 190*, 508–516.

Tylee, D. S., Sun, J., Hess, J. L., Tahir, M. A., Sharma, E., Malik, R., ... & Glatt, S. J. (2016). Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. *BioRxiv*, 070730.

Vaghi, M. M., Vértes, P. E., Kitzbichler, M. G., Apergis-Schoute, A. M., van der Flier, F. E., Fineberg, N. A., ... & Robbins, T. W. (2017). Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-

compulsive disorder: evidence from resting-state functional connectivity. *Biological Psychiatry, 81*(8), 708–717.

Vaidyanathan, U., Malone, S. M., Donnelly, J. M., Hammer, M. A., Miller, M. B., McGue, M., & Iacono, W. G. (2014). Heritability and molecular genetic basis of antisaccade eye tracking error rate: A genome-wide association study. *Psychophysiology, 51*(12), 1272–1284.

Valdar, W., Solberg, L. C., Gauguier, D., Burnett, S., Klenerman, P., Cookson, W. O., ... & Flint, J. (2006). Genome-wide genetic association of complex traits in heterogeneous stock mice. *Nature Genetics, 38*, 879–887.

van den Heuvel, O. A., Remijnse, P. L., Mataix-Cols, D., Vrenken, H., Groenewegen, H. J., Uylings, H. B., ... & Veltman, D. J. (2009). The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain, 132*(4), 853–868.

van den Heuvel, O. A., van der Werf, Y. D., Verhoef, K. M., de Wit, S., Berendse, H. W., Wolters, E. C., ... & Groenewegen, H. J. (2010). Frontal–striatal abnormalities underlying behaviours in the compulsive–impulsive spectrum. *Journal of the Neurological Sciences, 289*(1), 55–59.

van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Cath, D. C., van Balkom, A. J., van Hartskamp, J., ... & van Dyck, R. (2005). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder*. Archives of General Psychiatry, 62*(3), 301–309.

van der Lee, S. J., Roshchupkin, G. V., Adams, H. H., Schmidt, H., Hofer, E., Saba, Y., ... & Niessen, W. J. (2017). Gray matter heritability in family-based and population-based studies using voxel-based morphometry. *Human Brain Mapping, 38*(5), 2408–2423.

van der Wee, N. J., Hardeman, H. H., Ramsey, N. F., Raemaekers, M., Van Megen, H. J., Denys, D. A., ... & Kahn, R. S. (2006). Saccadic abnormalities in psychotropic-naive obsessive–compulsive disorder without co-morbidity. *Psychological Medicine, 36*(9), 1321–1326.

van Grootheest, D. S., Bartels, M., Van Beijsterveldt, C. E., Cath, D. C., Beekman, A. T., Hudziak, J. J., & Boomsma, D. I. (2008). Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. Journal of the American Academy of Child & Adolescent Psychiatry, 47(10), 1182–1188.

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2007). Genetic and environmental contributions underlying stability in childhood obsessive-compulsive behavior. *Psychological Medicine, 37,* 1635–1644.

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2005). Twin studies on obsessive–compulsive disorder: a review. *Twin Research and Human Genetics, 8*(5), 450–458.

van Kampen, D., & Deijen, J. B. (2009). SPEM dysfunction and general schizotypy as measured by the SSQ: a controlled study. *BMC Neurology, 9*(1), 27.

Vergilino-Perez, D., Fayel, A., Lemoine, C., Senot, P., Vergne, J., & Doré-Mazars, K. (2012). Are there any left-right asymmetries in saccade parameters? Examination of latency, gain, and peak velocity. *Investigative Ophthalmology & Visual Science, 53*(7), 3340–3348

Verweij, K. J., Zietsch, B. P., Medland, S. E., Gordon, S. D., Benyamin, B., Nyholt, D. R., ... & Wray, N. R. (2010). A genome-wide association study of Cloninger's temperament scales: implications for the evolutionary genetics of personality. *Biological Psychology, 85*(2), 306–317.

Viswanath, B., Reddy, Y. J., Kumar, K. J., Kandavel, T., & Chandrashekar, C. R. (2009). Cognitive endophenotypes in OCD: a study of unaffected siblings of probands with familial OCD. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33*(4), 610–615.

Vollema, M. G., & van den Bosch, R. J. (1995). The multidimensionality of schizotypy. *Schizophrenia Bulletin, 21*(1), 19–31.

Waddington, C. H. (1956). Embryology, epigenetics and biogenetics. *Nature, 177*(4522), 1241.

Wang, Y., Liu, W. H., Li, Z., Wei, X. H., Jiang, X. Q., Neumann, D. L., ... & Chan, R. C. (2015). Dimensional schizotypy and social cognition: an fMRI imaging study. *Frontiers in Behavioral Neuroscience, 9*, 133.

Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Lee, C. K., ... & Wittchen, H. U. (1994). The cross national epidemiology of obsessive-compulsive disorder. *Journal of Clinical Psychiatry, 55*(3 Suppl.), 5–10.

Weissman, M. M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., & Olfson, M. (2000). Brief screening for family psychiatric history: the family history screen. *Archives of General Psychiatry, 57*(7), 675–682.

Welch, J. M., Lu, J., Rodriguiz, R. M., Trotta, N. C., Peca, J., Ding, J. D., ... & Feng, G. (2007). Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature, 448*(7156), 894–900.

Whiteside, S. P., Port, J. D., & Abramowitz, J. S. (2004). A meta–analysis of functional neuroimaging in obsessive–compulsive disorder. *Psychiatry Research: Neuroimaging, 132*(1), 69–79.

Williams, J. T., & Blangero, J. (2004). Power of variance component linkage analysis—II. Discrete traits. *Annals of Human Genetics, 68*(6), 620–632.

Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H. J., Hill, A., Gast, U., ... & Driessen, M. (2010). The German version of the Childhood Trauma Questionnaire (CTQ): preliminary psychometric properties. Psychotherapie, Psychosomatik, *Medizinische Psychologie, 60*(11), 442–450.

Witiuk, K., Fernandez-Ruiz, J., McKee, R., Alahyane, N., Coe, B. C., Melanson, M., & Munoz, D. P. (2014). Cognitive deterioration and functional compensation in ALS measured with fMRI using an inhibitory task. *Journal of Neuroscience, 34*(43), 14260–14271.

Wittchen, H. U., Zaudig, M., & Fydrich, T. (1997). *SKID. Strukturiertes klinisches Interview für DSM-IV. Achse I und II. Handanweisung*. Göttingen, Germany: Hogrefe.

Wood, A. R., Esko, T., Yang, J., Vedantam, S., Pers, T. H., Gustafsson, S., ... & Frayling, T. M. (2014). Defining the role of common variation in the genomic and biological architecture of adult human height. *Nature Genetics, 46*(11), 1173–1186.

Yamamoto, H., Tsuchida, H., Nakamae, T., Nishida, S., Sakai, Y., Fujimori, A., … Fukui, K. (2012). Relationship between severity of obsessive-compulsive symptoms and schizotypy in obsessive-compulsive disorder. *Neuropsychiatric Disease and Treatment, 8*, 579–83.

Yasuda, Y., Hashimoto, R., Ohi, K., Fukumoto, M., Umeda-Yano, S., Yamamori, H., ... & Takeda, M. (2011). Impact on schizotypal personality trait of a genome-wide supported psychosis variant of the ZNF804A gene. *Neuroscience Letters, 495*(3), 216–220.

Yuan, M., & Diao, G. (2011). Joint association analysis of bivariate quantitative and qualitative traits. *BMC, 5*(Suppl 9), S74.

Zhang, L., Dong, Y., Ji, Y., Zhu, C., Yu, F., Ma, H., ... & Wang, K. (2015). Dissociation of decision making under ambiguity and decision making under risk: A neurocognitive endophenotype candidate for obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 57*, 60–68.

Zisner, A., & Beauchaine, T. P. (2016). Neural substrates of trait impulsivity, anhedonia, and irritability: Mechanisms of heterotypic comorbidity between externalizing disorders and unipolar depression. *Development and Psychopathology*, 28(4pt1), 1177–1208.

Zobel, A., & Maier, W. (2004). Endophenotype--a new concept for biological characterization of psychiatric disorders. *Der Nervenarzt, 75*(3), 205–214.

Zohar, A. H. (1999). The epidemiology of obsessive-compulsive disorder in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America, 8*(3), 445–460.

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Harm avoidance and childhood adversities in patients with obsessive–compulsive disorder and their unaffected first-degree relatives

Bey K, Lennertz L, Riesel A, Klawohn J, Kaufmann C, Heinzel S, Grützmann R, Kathmann N, Wagner M. Harm avoidance and childhood adversities in patients with obsessive–compulsive disorder and their unaffected first-degree relatives.

Objective: The etiology of obsessive–compulsive disorder (OCD) is assumed to involve interactions between genetically determined vulnerability factors and significant environmental features. Here, we aim to investigate how the personality trait harm avoidance and the experience of childhood adversities contribute to OCD.
Method: A total of 169 patients with OCD, 157 healthy comparison subjects, and 57 unaffected first-degree relatives of patients with OCD participated in the study. Harm avoidance was assessed using the Temperament and Character Inventory, and the severity of childhood adversities was measured with the Childhood Trauma Questionnaire.
Results: Both patients with OCD and relatives showed elevated levels of harm avoidance compared to controls. Furthermore, patients exhibited significantly higher scores than relatives. This linear pattern was observed throughout all subscales of harm avoidance, and remained stable after controlling for the severity of depressive and obsessive–compulsive symptoms. With regard to childhood adversities, patients with OCD reported higher levels than relatives and controls.
Conclusion: Our results provide further evidence for a diathesis-stress model of OCD. While patients and unaffected relatives share elevated levels of harm avoidance, supporting the role of harm avoidance as an endophenotype of OCD, a heightened severity of childhood adversity was only observed in patients. The assumed biological underpinnings of these findings are discussed.

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Key words: obsessive–compulsive disorder; harm avoidance; childhood adversity; Childhood Trauma Questionnaire; endophenotype

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Significant outcomes

- Predisposing personality traits and critical environmental factors interactively contribute to the etiology of obsessive–compulsive disorder (OCD).
- Harm avoidance represents a potential endophenotype of OCD, which may aid the discovery of genetic variants underlying OCD.

Limitations

- The findings are based on cross-sectional data. Childhood adversity was assessed retrospectively.
- Unaffected relatives were not well-matched to patients with obsessive–compulsive disorder (OCD) and healthy volunteers regarding age and gender.
- It cannot be concluded that the present findings are specific to OCD.

Introduction

Obsessive–compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors), which affects 1–3% of the population worldwide (1). OCD is familial, with first-degree relatives having a five-fold increased risk on average to also be affected with the disease (2–4). Twin studies of OCD and OCD-related traits yield heritability estimates around 50% (5, 6). Similar to the majority of psychiatric disorders, OCD's etiology is assumed to involve interactions between genetically determined vulnerability factors and significant environmental features. More specifically, anxiety-related personality traits such as harm avoidance constitute important predispositions, while childhood adversities represent critical life events.

Harm avoidance is a personality trait characterized by excessive worrying, fear of uncertainty, shyness, and fatigability. Conceptualized as a temperament dimension in Cloninger's biosocial model of personality (7), it is referred to as an automatic tendency to respond intensely to aversive stimuli. With heritability estimates ranging from 42% to 57%, harm avoidance has a strong genetic contribution (8–10) and is highly stable throughout life (11). In line with Cloninger's and Svrakic's (12) proposal that individual configurations in personality structure influence the risk of psychopathology, high levels of harm avoidance have repeatedly been associated with various psychiatric disorders, including OCD (13–16). Importantly, harm avoidance is not a mere epiphenomenon of psychopathology, as fully remitted patients with depression (17, 18) and eating disorders (19) still exhibit elevated harm avoidance scores, and the extent of harm avoidance predicted depression 5 years later in a sample of 14-year-old children (20). In patients with OCD, harm avoidance scores reduce in response to treatment, but still remain significantly elevated compared to healthy volunteers (21). Furthermore, evidence from a large cohort study shows that subjects who met the diagnostic criteria of OCD at the age of 26 or 32 already exhibited heightened levels of negative emotionality at the age of 18 (22), supporting the notion that traits associated with negative emotionality constitute premorbid vulnerability factors. Most notably, increased levels of harm avoidance have also been observed in first-degree relatives of patients with OCD, indicating that harm avoidance may partially mediate the familial risk for OCD (15, 23). In the same line, both patients with OCD and unaffected relatives show elevated scores of neuroticism (24), which is strongly correlated with harm avoidance (25).

On the other hand, traumatic life events, particularly childhood maltreatment, may represent a common developmental origin to adult psychiatric disorders (26, 27). Accordingly, stressful and traumatic life events have been linked to OCD symptoms (28, 29), and patients with OCD report more childhood adversities than matched healthy comparison subjects, especially in the domains of emotional abuse and emotional neglect (30, 31). Several cases have been published describing an onset of OCD with timing and symptoms suggestive of a traumatic etiology (32, 33), supporting the assumption of a causal link between traumatic events and the occurrence of OCD (34). Still, traumatic factors may be important in some, but not all cases of OCD (35). The impact of childhood trauma appears to depend on the presence of genetically determined vulnerability factors, as indicated by recent research reporting significant interactions between adverse childhood experiences and genetic variation in the BDNF, COMT, MAO A, and MAO B genes on OCD risk (31, 36). Further evidence for a gene–environment interaction comes from a study on obsessive–compulsive traits in monozygous twins showing that differences within pairs discordant for obsessive-compulsive traits were accounted for by a relatively high frequency of sexual assault experienced by the high-scoring twins of the discordant pairs in comparison with their low-scoring twin siblings (37).

Aims of the study

In this study, we aim to investigate how childhood adversities and harm avoidance contribute to obsessive–compulsive disorder (OCD) liability by assessing a large sample of patients with OCD, unaffected first-degree relatives and healthy comparison subjects. As the association between childhood adversity and OCD appears to be modulated by genetic variation, and harm avoidance constitutes one of the most promising endophenotype candidates indicating OCD vulnerability, we considered this trait a fruitful target for our analyses. Against the background of a diathesis-stress model, we assumed that both patients and relatives would show elevated levels of harm avoidance compared to healthy volunteers, representing an underlying vulnerability. Conversely, childhood adversities were hypothesized to only be elevated in patients, but not in relatives. Furthermore, patients were expected to show higher harm avoidance scores than relatives as an expression of their

psychopathological state and potential modulation due to childhood adversities.

Material and methods

Participants

One hundred and sixty-nine patients with OCD, 157 healthy comparison subjects, and 57 unaffected first-degree relatives of patients with OCD ($n = 37$ parents, $n = 18$ siblings, and $n = 2$ offspring) participated in the study. Patients and controls were matched for age and gender, while relatives were significantly older than patients and controls, with a trend toward a greater proportion of women (see Table 1 for sample characteristics). Patients with OCD and relatives were recruited via the out-patient clinics at the Department of Psychology of Humboldt University Berlin and at the Department of Psychiatry and Psychotherapy of the University of Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements.

All participants were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV (SCID-I) (38, 39). Patients and relatives were only included if they were (i) free of past or present psychotic, bipolar, or substance related disorders; (ii) did not take neuroleptic medication in the past 4 weeks; and (iii) did not use benzodiazepines in the past 2 weeks. Additionally, healthy controls were excluded if they (i) took any psychoactive medication in the past 3 months, (ii) had a current axis-I disorder, (iii) lifetime diagnosis of OCD or tic disorder, or (iv) a family history of OCD. All relatives were free of past or present OCD.

Eighty-one patients with OCD were medicated, with $n = 64$ taking selective serotonin reuptake inhibitors and $n = 31$ taking other antidepressants. Sixty-three patients were medication-naive. Furthermore, the majority of patients had one or more current comorbid axis-I disorders, that is, major depression ($n = 43$ current episode, $n = 82$ remitted), dysthymia ($n = 14$), panic disorder with agoraphobia ($n = 2$), panic disorder without agoraphobia ($n = 2$), social phobia ($n = 12$), specific phobia ($n = 13$), generalized anxiety disorder ($n = 6$), posttraumatic stress disorder ($n = 3$), attention deficit/hyperactivity disorder ($n = 1$), anorexia nervosa ($n = 1$), binge eating disorder ($n = 2$), tic disorder ($n = 12$), skin picking disorder ($n = 9$), hypochondria ($n = 2$), body dysmorphic disorder ($n = 3$), hoarding disorder ($n = 2$), pain disorder ($n = 2$), and unspecific somatoform disorder ($n = 5$).

Written informed consent was obtained, and participants were compensated for their time. The study was in accordance with the revised Declaration of Helsinki and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Clinic Bonn.

Measures

Harm avoidance was assessed using the German version of the Temperament and Character Inventory (TCI) (40, 41). For each subject, a sum score was computed based on the 35 binary items of the harm avoidance scale. Cronbach's α of the global scale was $\alpha = 0.92$, indicating high internal consistency. Reliability analyses of the four subscales yielded $\alpha = 0.81$ for anticipatory worry, $\alpha = 0.71$ for fear of uncertainty, $\alpha = 0.77$ for shyness, and $\alpha = 0.82$ for fatigability.

The Childhood Trauma Questionnaire (CTQ) (42, 43) is a retrospective self-report inventory that measures the severity of different types of childhood trauma, that is, emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, and the experience of inconsistencies (34-item version) (44). The measure also includes a three-item minimization/denial scale indicating the potential underreporting of maltreatment. In this study, internal consistencies were high for the

Table 1. Demographic and clinical characteristics of patients with OCD, unaffected first-degree relatives, and healthy control subjects

	Patients with OCD	Unaffected first-degree relatives	Healthy control subjects	Statistic	*P*
N	169	57	157		
Mean age, years (SD)	32.89 (10.34)	47.75 (14.36)	34.32 (12.90)	$F(2, 374) = 33.84$	<0.001
Gender (% male)	43.4	26.3	35.7	$\chi^2(2) = 5.68$	0.058
Mean OCI-R score (SD)	27.59 (12.37)	7.47 (7.94)	4.52 (4.66)	$F(2, 380) = 275.28$	<0.001
Mean BDI-II score (SD)	19.14 (10.56)	7.07 (7.20)	2.85 (4.17)	$F(2, 380) = 175.48$	<0.001
Mean Y-BOCS score (SD)*	22.31 (6.57)				
Mean age of onset (SD)*	20.95 (10.74)				

BDI-II, Beck Depression Inventory-II; OCD, obsessive–compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; SD, Standard Deviation; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

*Y-BOCS and age of onset were only applicable in patients.

global CTQ scale ($\alpha = 0.90$) and for all subscales ($\alpha = 0.87$ for emotional abuse, $\alpha = 0.74$ for physical abuse, $\alpha = 0.93$ for sexual abuse, $\alpha = 0.89$ for emotional neglect, $\alpha = 0.74$ for minimization/denial, $\alpha = 0.82$ for experience of inconsistencies) except for physical neglect ($\alpha = 0.35$), which was hence not considered for subscale analyses.

The severity of OCD symptoms was assessed using the German versions of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (45, 46) and the Obsessive-Compulsive Inventory-Revised (OCI-R) (47, 48). OCD symptom dimensions were measured via the Y-BOCS Symptom Checklist (Y-BOCS CL) (45). The Beck Depression Inventory-II (BDI-II) (49, 50) was employed to assess the severity of current depressive symptoms.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Release 23.0 (SPSS Inc., Chicago, IL, USA). To test for group differences in harm avoidance and childhood adversities between patients with OCD, unaffected first-degree relatives and healthy controls, analyses of variance (ANOVAS) were conducted. We investigated global scores as well as subscales. Significant main effects were further examined using Tukey's tests. Moreover, analyses of covariance (ANCOVAS) were conducted to investigate whether group differences in harm avoidance were accounted for by the severity of depressive or obsessive–compulsive symptoms. To test whether the interaction between harm avoidance and CTQ scores significantly predicts caseness (patient with OCD/unaffected relative/control subject), a multinominal logistic regression was performed.

Associations with specific OCD symptom dimensions were investigated using the Y-BOCS CL. Following the procedure established in previous studies (51, 52), the 13 main categories of the Y-BOCS CL were coded as 1 if the patient reported having experienced at least one symptom of the respective category. Else, the category was coded as 0. These binary variables were then fed into an exploratory principal component analysis with varimax rotation. Factors were extracted based on the Kaiser-Guttmann criterion, that is, eigenvalue (EV) > 1. For each patient with OCD, factor scores were exported to use in further analyses. Each of the scores was standardized to a mean of 0 and a standard deviation of 1.

Pearson's correlation coefficients were computed to explore relationships between harm avoidance, childhood adversities, depressive symptoms, OCD severity, and symptom dimension scores. Group differences in demographic and clinical characteristics were tested using ANOVAS, and Fisher's chi-square test was used to compare sex ratios among groups. As relatives were significantly older [$F(2, 371) = 34.38$, $P < 0.001$] and showed a trend toward less male subjects [$\chi^2(2) = 5.68$, $P = 0.058$] compared to patients with OCD and control subjects, all analyses were run with and without the inclusion of age and gender as covariates. As none of the group effects reported below was altered by the inclusion of these covariates, and for the sake of clarity, we only report results from the analyses without covariates in the main text. Results from the ANCOVAS including age and gender can be found in Appendix S1. Furthermore, we performed exploratory ANOVAS using medication (any psychoactive medication within the past 4 weeks vs. previous medication but not in the past 4 weeks vs. medication-naive), current depressive comorbidity, and age of onset (≤18 vs. >18) as between-subjects factor in OCD subjects, and relation (parents vs. siblings) in relatives. The alpha level was set at 0.05 for all statistical analyses.

Results

Clinical characteristics

Demographical and clinical characteristics are given in Table 1. Groups significantly differed regarding OCI-R [$F(1, 380) = 611.66$, $P < 0.001$] and BDI-II [$F(1, 380) = 442.01$, $P < 0.001$]. Post hoc contrasts revealed that patients with OCD reported significantly higher OCI-R scores than unaffected relatives and control subjects (both $P < 0.001$). Notably, unaffected relatives showed a trend toward heightened levels of obsessive–compulsive symptoms as compared to healthy volunteers ($P = 0.099$). With respect to depressive symptoms, patients with OCD showed significantly higher BDI-II scores than both of the other groups (both $P < 0.001$). Yet, relatives also exhibited elevated scores compared to controls ($P = 0.002$).

Group differences in harm avoidance

Groups significantly differed with respect to the global harm avoidance score [$F(2, 380) = 160.48$, $P < 0.001$] (Fig. 1). Tukey's tests revealed that both patients with OCD and relatives showed significantly higher levels of harm avoidance than healthy volunteers (both $P < 0.001$). Furthermore, patients reported significantly higher scores than relatives ($P < 0.001$). This linear pattern was observed in each of the four subscales [$F(2, 380) = 116.30$, $P < 0.001$ for anticipatory

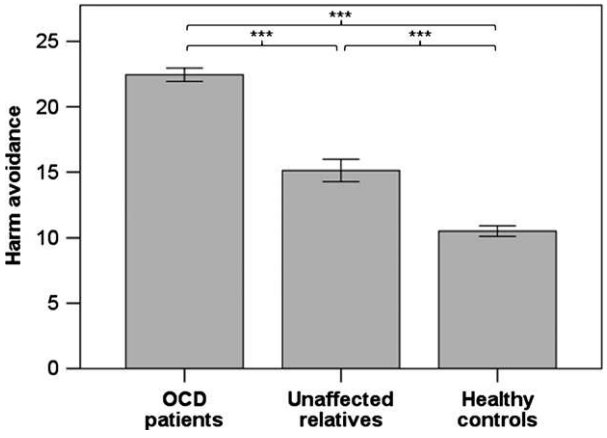

Fig. 1. Elevated levels of harm avoidance in patients with OCD and unaffected first-degree relatives compared to healthy control subjects. Error bars indicate standard errors. OCD, obsessive–compulsive disorder. ***$P < 0.001$.

worry; $F(2, 380) = 83.29$, $P < 0.001$ for fear of uncertainty; $F(2, 380) = 63.18$, $P < 0.001$ for shyness; $F(2, 380) = 120.59$, $P < 0.001$ for fatigability].

Parents and siblings of patients with OCD did not differ regarding their levels of harm avoidance [$F(1, 53) = 0.09$, $P = 0.76$]. Notably, however, patients with current comorbid depression showed significantly higher levels of harm avoidance than patients without depression [$F(1, 158) = 8.51$, $P = 0.004$].

As the severity of depressive symptoms was strongly related to harm avoidance (see section Associations between harm avoidance, childhood adversity, depressive, and obsessive–compulsive symptoms), an ANCOVA was conducted to investigate whether the group difference in harm avoidance was accounted for by BDI-II scores. The pattern of patients with OCD > unaffected relatives > healthy controls persisted [$F(2, 379) = 26.38$, $P < 0.001$] even after controlling for depressive symptom severity [$F(1, 379) = 130.24$, $P < 0.001$]. A second ANCOVA controlling for OCI-R scores yielded similar results [OCI-R effect: $F(1, 379) = 34.40$, $P < 0.001$; group effect: $F(2, 379) = 32.41$, $P < 0.001$].

Furthermore, the results did not change when patients with any comorbid anxiety disorder were excluded from the analysis [$F(2, 351) = 128.76$, $P < 0.001$]. There was neither an effect of medication [$F(2, 166) = 2.32$, $P = 0.10$] nor age of onset [$F(1, 149) = 0.53$, $P = 0.47$].

Group differences in childhood adversities

The severity of childhood adversities differed significantly between groups [$F(2, 378) = 5.73$, $P = 0.004$] (Fig. 2). As indicated by post hoc contrasts, patients with OCD exhibited significantly higher scores than unaffected relatives and healthy volunteers ($P = 0.015$ and $P = 0.016$ respectively), while there was no difference between relatives and controls ($P = 0.71$). Analyses of subscales indicated that this effect was driven by emotional abuse [$F(2, 378) = 6.12$, $P = 0.002$], emotional neglect [$F(2, 378) = 4.53$, $P = 0.011$], and the experience of inconsistencies [$F(2, 378) = 9.35$, $P < 0.001$]. There were no significant group differences in physical abuse [$F(2, 378) = 2.32$, $P = 0.10$], sexual abuse [$F(2, 378) = 0.48$, $P = 0.62$], and minimization/denial [$F(2, 378) = 0.17$, $P = 0.84$].

Subgroup analyses indicated that the severity of childhood adversities did neither differ between OCD patients with and without comorbid depression [$F(1, 156) = 0.32$, $P = 0.58$], nor between parents and siblings of patients with OCD [$F(1, 53) = 1.91$, $P = 0.17$]. The effects remained stable when patients with any comorbid anxiety disorder were excluded [$F(2, 349) = 4.01$, $P = 0.019$]. Medication status [$F(2, 164) = 0.30$, $P = 0.74$] and age of onset [$F(1, 149) = 0.13$, $P = 0.72$] were also not associated with CTQ scores.

Predicting caseness based on the interaction between harm avoidance and childhood adversity

As indicated by the likelihood ratio chi-square test in the multinominal logistic regression, the interaction between harm avoidance and CTQ scores significantly predicted caseness [$\chi^2(2) = 154.64$, $P < 0.001$], with a Nagelkerke's pseudo R^2 of 0.38.

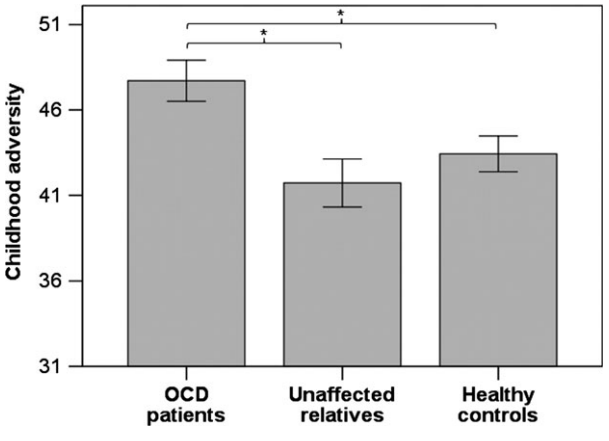

Fig. 2. Higher severity of childhood adversity in patients with OCD compared to unaffected first-degree relatives and healthy control subjects. Error bars indicate standard errors. OCD, obsessive–compulsive disorder. *$P < 0.05$.

Associations between harm avoidance, childhood adversity, depressive, and obsessive–compulsive symptoms

Results from the correlation analyses are presented in Table 2. We observed a significant correlation between the severity of childhood adversities and harm avoidance in patients with OCD ($r = 0.18$, $P = 0.021$), unaffected relatives ($r = 0.35$, $P = 0.008$), and healthy controls ($r = 0.23$, $P = 0.004$). Furthermore, harm avoidance was strongly related to BDI-II scores across groups ($r = 0.56$, $P < 0.001$ in patients; $r = 0.60$, $P < 0.001$ in relatives; $r = 0.33$, $P < 0.001$ in controls). In patients, harm avoidance was significantly correlated with OCD severity as assessed with Y-BOCS ($r = 0.32$, $P < 0.001$) and OCI-R ($r = 0.36$, $P < 0.001$). Interestingly, OCI-R scores were also associated with harm avoidance in relatives ($r = 0.29$, $P = 0.027$), but not in healthy controls ($r = 0.09$, $P = 0.28$). While CTQ scores were significantly correlated with depressive symptoms ($r = 0.24$, $P = 0.002$ in patients; $r = 0.35$, $P = 0.008$ in relatives; $r = 0.35$, $P < 0.001$ in controls), there was no association of childhood adversity with OCI-R ($r = 0.11$, $P = 0.16$ in patients; $r = 0.21$, $P = 0.12$ in relatives; $r = 0.15$, $P = 0.069$ in controls) and Y-BOCS scores ($r = 0.01$, $P = 0.92$).

Symptom dimensions

Principal component analysis yielded four factors representing the dimensions symmetry/ordering (symmetry/ordering/counting/repeating; EV = 3.10) obsessions/checking (aggressive/sexual/religious/somatic/checking; EV = 1.64), washing/contamination (EV = 1.31), and hoarding (hoarding obsessions/hoarding compulsions; EV = 1.24). Together, these factors explained 56.12% of variance in OCD symptom dimensions. The patients' factor scores for obsessions/checking and washing/contamination were significantly correlated with harm avoidance ($r = 0.33$, $P < 0.001$ and $r = 0.16$, $P = 0.034$ respectively), whereas symmetry/ordering ($r = 0.11$, $P = 0.14$) and hoarding ($r = 0.03$, $P = 0.68$) were not related to harm avoidance. Although the OCD symptom dimension scores showed no substantial associations with the global CTQ score, obsessions/checking was significantly related to each of the three abuse subscales, that is, physical abuse ($r = 0.24$, $P = 0.002$), emotional abuse ($r = 0.18$, $P = 0.019$), and sexual abuse ($r = 0.17$, $P = 0.027$). All other correlations between OCD symptom dimensions and CTQ subscales did not reach significance (all $|r| < 0.15$, $P > 0.05$).

Discussion

The results of the present study support the roles of harm avoidance and childhood adversities as important etiological factors of OCD. In a large sample, we found that patients with OCD as well as their unaffected first-degree relatives exhibit elevated levels of harm avoidance compared to healthy control subjects, which were neither accounted for by the severity of depressive symptoms nor by the extend of obsessive–compulsive symptoms. A linear pattern of patients with OCD > unaffected relatives > healthy controls was observed throughout all harm avoidance subscales. Furthermore, patients with OCD reported more severe childhood adversities than unaffected relatives and healthy volunteers. Consistent with

Table 2. Pearson's correlations between harm avoidance, childhood adversity, depressive and obsessive–compulsive symptoms in patients with OCD, unaffected first-degree relatives, and healthy control subjects

	TCI HA	CTQ	BDI-II	OCI-R
Patients with OCD				
CTQ	**$r = 0.18$, $P = 0.021$**			
BDI-II	**$r = 0.56$, $P < 0.001$**	**$r = 0.24$, $P = 0.002$**		
OCI-R	**$r = 0.36$, $P < 0.001$**	$r = 0.11$, $P = 0.16$	**$r = 0.36$, $P < 0.001$**	
Y-BOCS*	**$r = 0.32$, $P < 0.001$**	$r = 0.01$, $P = 0.92$	**$r = 0.42$, $P < 0.001$**	**$r = 0.51$, $P < 0.001$**
Unaffected first-degree relatives				
CTQ	**$r = 0.35$, $P = 0.008$**			
BDI-II	**$r = 0.60$, $P < 0.001$**	**$r = 0.35$, $P = 0.008$**		
OCI-R	**$r = 0.29$, $P = 0.027$**	$r = 0.21$, $P = 0.12$	**$r = 0.46$, $P < 0.001$**	
Healthy control subjects				
CTQ	**$r = 0.23$, $P = 0.004$**			
BDI-II	**$r = 0.33$, $P < 0.001$**	**$r = 0.35$, $P < 0.001$**		
OCI-R	$r = 0.09$, $P = 0.28$	$r = 0.15$, $P = 0.069$	**$r = 0.44$, $P < 0.001$**	

BDI-II, Beck's Depression Inventory-II; CTQ, Childhood Trauma Questionnaire; OCD, obsessive–compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; TCI HA, harm avoidance scale of the Temperament and Character Inventory; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

Significant correlations are printed in bold.

*Y-BOCS was only assessed in patients.

previous research, this effect was driven by the subscales emotional abuse and emotional neglect (30, 31). The experience of inconsistencies also emerged to be an important aspect of childhood adversity associated with OCD.

Taken together, the present findings support the notion of a diathesis-stress model of OCD. In this model, harm avoidance represents an underlying vulnerability factor, which may contribute to the development of OCD in interaction with adverse childhood experiences.

More specifically, harm avoidance appears to constitute an endophenotype of OCD, which is a quantitative variable characterized by specific criteria (53): An endophenotype must (i) be heritable; (ii) be associated with the illness; (iii) be independent of clinical state; (iv) co-segregate with the illness within a family (i.e. unaffected relatives are expected to show abnormalities similar to those observed in patients); and (v) represent reproducible measurements (54, 55). Converging evidence from the present study and previous research indicates that harm avoidance meets each of these criteria: (i) with heritability estimates ranging from 42% to 57%, harm avoidance has a strong genetic component (8–10); (ii) elevated levels of harm avoidance have repeatedly been observed in patients with OCD (15, 16); (iii) although harm avoidance scores are correlated with OCD severity and reduce after successful treatment, they remain significantly elevated compared to healthy volunteers (21); (iv) first-degree relatives of patients with OCD show higher levels of harm avoidance than healthy subjects from the general population (15, 23); and (v) harm avoidance is a highly stable and reliably measurable trait (11).

A predisposition to exaggerated anxiety responses facing unfamiliar or stressful situations and stimuli may take different trajectories depending on protective and adverse environmental influences. Early stressful life events may provoke alterations of the physiological stress response and thus of the hypothalamic–pituitary–adrenal (HPA) axis, which can endure during adulthood and predispose an individual to develop psychopathology (56). In fact, once the HPA axis is overactivated during developmental processes, it remains permanently unstable, overdriven, vulnerable, or dysfunctional (56, 57), possibly due to epigenetic mechanisms (58). For example, individuals with a history of childhood abuse display lower rates of glucocorticoid expression and altered methylation status of the neuron-specific glucocorticoid receptor promoter, as well as persistent hyperreactivity of the HPA axis and the autonomic nervous system (59, 60). Similarly, a higher cortisol response to the dexamethasone/corticotropin-releasing hormone test has been associated with higher levels of harm avoidance (61). However, the HPA axis is not the only system affected by early-life adversity. Childhood maltreatment is also associated with a chronic inflammatory state as indicated by increased levels of proinflammatory cytokine, C-reactive protein and fibrinogen (62), and marked gray matter abnormalities in right orbitofrontal and limbic regions, which are implicated in the pathophysiology of OCD (63). Most notably, a positive correlation between early-life adversity and right orbitofrontal volume has recently been observed in patients with OCD, indicating that neuroanatomical abnormalities may reflect underlying developmental neuropathology in adults with OCD who have experienced childhood trauma (64). Behaviorally, adverse effects of perinatal rearing experiences (e.g. maternal separation or loss, abuse or neglect, social deprivation) on anxiety- and depression-like behaviors have been demonstrated in both rodents and non-human primates, using prospective experimental study designs (65, 66).

The positive association between harm avoidance and the severity of childhood adversity across patients with OCD, relatives, and controls is consistent with previous observations in a large community-based sample of 12 225 subjects (60). Although a causal connection cannot be inferred from these cross-sectional data, it is conceivable that traumatic childhood experiences sustainably influence personality development and may thus contribute to psychopathology. Along these lines, Spinhoven et al. (67) report that the association between the severity of childhood maltreatment and higher levels of psychological distress is mediated by maladaptive personality types. Traumatic childhood experiences, specifically emotional abuse and neglect, may thus channel personality development toward a tendency to respond intensely to signals of aversive stimuli, making an individual learn to avoid punishment and potentially harmful situations by inhibiting behavior (68), which may eventually contribute to the development of OCD, anxiety, and mood disorders. In this regard, our results also highlight the importance of considering comorbid depressive symptoms, as they were related to both harm avoidance and childhood adversities across groups. Yet, group differences in harm avoidance were not accounted for by depressive symptoms, supporting the role of harm avoidance as an underlying vulnerability factor. Excluding patients with comorbid anxiety disorders did not change the results, either.

Moreover, age of onset was neither related to the severity of childhood adversities nor to levels of harm avoidance. This observation is in line with previous research reporting less parental warmth and more parental rejection in patients with OCD, independent of age of onset (69). Hence, OCD patients' elevated CTQ scores cannot exclusively be explained as a result of familial distress due to childhood-onset OCD.

Given the strong heterogeneity in OCD, we also explored different symptom dimensions. The results from our factor analysis are well in line with previous research (52, 70) and thus represent a valid basis for the correlational analyses, which yielded significant associations of harm avoidance with obsessions/checking and with washing/contamination, but neither with symmetry/ordering nor with hoarding. While the global CTQ score was not related to any of the four symptom dimensions, significant correlations were observed between obsessions/checking and the three abuse subscales, that is, emotional, physical, and sexual abuse. Although research addressing OCD symptom dimensions in relation to early-life adversity is scarce so far, the latter finding is in line with a study reporting a significant correlation between the obsessions/checking dimension and traumatic life events (29). The authors also observed an effect of symmetry/ordering, while no associations with washing/contamination and hoarding were found (29). Considering that obsessive–compulsive checkers, as compared to washers, show significantly worse task performance in a range of cognitive domains (71) as well as differences in brain anatomy (72), it may be hypothesized that these effects are mediated by the vast neuropathological effects of childhood maltreatment. This question should be addressed in future research. The finding that harm avoidance is especially implicated in obsessions/checking and washing/contamination symptoms contributes to the detailed characterization of OCD subtypes and may inform the tailoring of cognitive therapy.

The present study is not without limitations. First, despite the good consistency of self-reports of maltreatment over time (73), the CTQ is a retrospective inventory, whose validity may potentially be undermined by response biases (74). It cannot be excluded that patients judge their childhood experiences more negatively due to their psychopathological state. However, a study investigating remembered parental bonding in healthy subjects over the course of 20 years observed a high stability of reports, and changes of appraisal were unrelated to the severity of depressive symptoms (75). Likewise, Brewin et al. (76) conclude that claims concerning the general unreliability of retrospective reports are exaggerated and that there is little reason to link psychiatric status with less reliable or less valid recall of early experiences. Finally, there was no difference between patients with OCD, relatives and health controls regarding the minimization/denial scale in the present study, and scores were very low overall, indicating no evidence for an underreporting bias of maltreatment. A second limitation concerns the issue that unaffected relatives were not well-matched to patients with OCD and healthy volunteers regarding age and gender. As the inclusion of these factors as covariates did not change the main findings of the present study, we chose not to truncate our large sample for the attainment of perfectly matched groups. The ANCOVA results are included in the Supporting information for the sake of transparency. Third, we did not employ any scale measuring clinically relevant anxiety symptoms or perceived intensity and tolerability of daily-life stressors. It is possible that harm avoidance has no direct effect on OCD but contributes to the emergence of anxiety by biasing the appraisal of potentially threatening situations. However, excluding patients with comorbid anxiety disorders did not change our main findings, supporting the role of harm avoidance as a key feature of OCD. Fourth, it cannot be concluded that the present findings are specific to OCD. In fact, harm avoidance and other traits associated with negative emotionality show elevated levels in various psychiatric diseases (8–10), supporting the idea of a general vulnerability factor of psychopathology. Likewise, childhood adversity has not only been related to OCD but also to depression and a range of different anxiety disorders (77, 78). Future research may investigate whether the results reported here are specific to OCD or generalize to other psychiatric diseases.

Furthermore, it will be of great interest to explore the genetic and epigenetic underpinnings of the present findings. The identification of harm avoidance as an endophenotype of OCD may aid the discovery of genetic variants underlying OCD, as endophenotypes are supposed to depend upon variation in fewer genes than the more complex disease phenotype and may therefore be more tractable to genetic analysis (55). Support for common genetic effects among personality and mood, particularly neuroticism and depressive symptoms, has recently been found in terms of SNP association overlap and polygenic score prediction (79–81). The genetic overlap between harm avoidance and OCD, however, has not been investigated, yet, and should be addressed in future studies. With regard to epigenetics, patients with OCD show

significant alterations in the expression of specific microRNAs compared to healthy controls (82) and extensive differences in DNA methylation (83, 84). As recent evidence from an epigenome-wide study indicates that childhood trauma is associated with DNA methylation and cortisol stress reactivity (85), future research may explore whether the epigenetic alterations observed in OCD are mediated by adverse childhood experiences.

In conclusion, the present findings support the notion of a diathesis-stress model, in which predisposing and environmental factors interactively contribute to the etiology of OCD. While patients with OCD and unaffected first-degree relatives share elevated levels of harm avoidance, a heightened severity of childhood adversity was only observed in patients.

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Declarations of interest

The authors report no biomedical financial interests or potential conflict of interests.

References

1. Weissman MM, Bland RC, Canino GJ et al. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry 1994;**55**(Suppl.):5–10.
2. Grabe HJ, Ruhrmann S, Ettelt S et al. Familiarity of obsessive-compulsive disorder in nonclinical and clinical subjects. Am J Psychiatry 2006;**163**:1986–1992.
3. Nestadt G, Samuels J, Riddle M et al. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 2000;**57**:358–363.
4. Pauls DL, Alsobrook JP II, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. Am J Psychiatry 1995;**152**:76–84.
5. Nicolini H, Arnold P, Nestadt G, Lanzagorta N, Kennedy JL. Overview of genetics and obsessive-compulsive disorder. Psychiatry Res 2009;**170**:7–14.
6. Van Grootheest DS, Bartels M, Van Beijsterveldt CE et al. Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. J Am Acad Child Adolesc Psychiatry 2008;**47**:1182–1188.
7. Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry 1987;**44**:573–588.
8. Garcia D, Lundström S, Brändström S et al. Temperament and Character in the Child and Adolescent Twin Study in Sweden, CATSS: comparison to the general population, and genetic structure analysis. PLoS ONE 2013;**8**:e70475.
9. Gillespie NA, Cloninger CR, Heath AC, Martin NG. The genetic and environmental relationship between Cloninger's dimensions of temperament and character. Pers Individ Dif 2003;**35**:1931–1946.
10. Keller MC, Coventry WL, Heath AC, Martin NG. Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. Behav Genet 2005;**35**:707–721.
11. Josefsson K, Jokela M, Cloninger CR et al. Maturity and change in personality: developmental trends of temperament and character in adulthood. Dev Psychopathol 2013;**25**:713–727.
12. Cloninger CR, Svrakic DM. Integrative psychobiological approach to psychiatric assessment and treatment. Psychiatry 1997;**60**:120–141.
13. Richter MA, Summerfeldt LJ, Joffe RT, Swinson RP. The Tridimensional Personality Questionnaire in obsessive-compulsive disorder. Psychiatry Res 1996;**65**:185–188.
14. Fossey MD, Roy-Byrne PP, Cowley DS et al. Personality assessment using the Tridimensional Personality Questionnaire, TPQ in patients with panic disorder and generalized anxiety disorder. Biol Psychiatry 1989;**25**:10–13.
15. Ettelt S, Grabe HJ, Ruhrmann S et al. Harm avoidance in subjects with obsessive-compulsive disorder and their families. J Affect Disord 2008;**107**:265–269.
16. Kim SJ, Kang JI, Kim CH. Temperament and character in subjects with obsessive-compulsive disorder. Compr Psychiatry 2009;**50**:567–572.
17. Wilson S, Van Loo S, Geuens T, Claes SJ. Personality traits of patients who have recovered completely from depression. Tijdschr Psychiatr 2009;**52**:9–16.
18. Pelissolo A, Corruble E. Personality factors in depressive disorders: contribution of the psychobiologic model developed by Cloninger. Encephale 2001;**28**:363–373.
19. Bloks H, Hoek HW, Callewaert I, Van Furth E. Stability of personality traits in patients who received intensive treatment for a severe eating disorder. J Nerv Ment Dis 2004;**192**:129–138.
20. Ulrich I, Stopsack M, Spitzer C, Grabe HJ, Freyberger HJ, Barnow S. Familial transmission of depression: the importance of harm avoidance. Nervenarzt 2011;**82**:1169–1177.
21. Lyoo IK, Yoon T, Kang DH, Kwon JS. Patterns of changes in temperament and character inventory scales in subjects with obsessive-compulsive disorder following a 4-month treatment. Acta Psychiatr Scand 2003;**107**:298–304.
22. Grisham JR, Fullana MA, Mataix-Cols D, Moffitt TE, Caspi A, Poulton R. Risk factors prospectively associated with adult obsessive-compulsive symptom dimensions and obsessive-compulsive disorder. Psychol Med 2011;**41**:2495–2506.
23. Calvo R, Lázaro L, Castro-Fornieles J, Font E, Moreno E, Toro J. Obsessive-compulsive personality disorder traits and personality dimensions in parents of children with obsessive-compulsive disorder. Eur Psychiatry 2009;**24**:201–206.
24. Samuels J, Nestadt G, Bienvenu OJ et al. Personality disorders and normal personality dimensions in obsessive—compulsive disorder. Br J Psychiatry 2000;**177**:457–462.
25. Weyers P, Krebs H, Janke W. Reliability and construct validity of the German version of Cloninger's Tridimensional Personality Questionnaire. Pers Individ Dif 1995;**19**:853–861.
26. Keyes KM, Eaton NR, Krueger RF et al. Childhood maltreatment and the structure of common psychiatric disorders. Br J Psychiatry 2012;**200**:107–115.
27. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med 2012;**9**:e1001349.

28. Gothelf D, Aharonovsky O, Horesh N, Carty T, Apter A. Life events and personality factors in children and adolescents with obsessive-compulsive disorder and other anxiety disorders. Compr Psychiatry 2004;**45**:192–198.
29. Cromer KR, Schmidt NB, Murphy DL. An investigation of traumatic life events and obsessive-compulsive disorder. Behav Res Ther 2007;**45**:1683–1691.
30. Lochner C, Seedat S, Allgulander C, Kidd M, Stein D, Gerdner A. Childhood trauma in adults with social anxiety disorder and panic disorder: a cross-national study. Afr J Psychiatry (Johannesbg) 2010;**13**:376–381.
31. Hemmings SMJ, Lochner C, Van Der Merwe L, Cath DC, Seedat S, Stein DJ. BDNF Val66Met modifies the risk of childhood trauma on obsessive-compulsive disorder. J Psychiatr Res 2013;**47**:1857–1863.
32. De Silva P, Marks M. The role of traumatic experiences in the genesis of obsessive-compulsive disorder. Behav Res Ther 1999;**37**:941–951.
33. Sasson Y, Dekel S, Nacasch N et al. Posttraumatic obsessive compulsive disorder: a case series. Psychiatry Res 2005;**135**:145–152.
34. Lafleur DL, Petty C, Mancuso E et al. Traumatic events and obsessive compulsive disorder in children and adolescents: is there a link? J Anxiety Disord 2011;**25**:513–519.
35. Fontenelle LF, Cocchi L, Harrison BJ. Towards a posttraumatic subtype of obsessive-compulsive disorder. J Anxiety Disord 2012;**26**:377–383.
36. McGregor NW, Hemmings SM, Erdman L, Calmarza-Font I, Stein DJ, Lochner C. Modification of the association between early adversity and obsessive-compulsive disorder by polymorphisms in the MAOA, MAOB and COMT genes. Psychiatry Res 2016;**246**:527–532.
37. Cath DC, Van Grootheest DS, Willemsen G, Van Oppen P, Boomsma DI. Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins. Behav Genet 2008;**38**:108–120.
38. First MB, Spitzer RL, Gibbon M, Williams J. Structured clinical interview for DSM-IV axis I disorders, SCID, clinician version: user's guide. Washington, DC: American, Psychiatric Press, 1996.
39. Wittchen H, Zaudig M, Fydrich T. Strukturiertes Klinisches Interview für DSM-IV. Göttingen: Hogrefe, 1997.
40. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;**50**:975–990.
41. Richter J, Eisemann M, Richter G. German version of the temperament and character inventory. Z Klein Psychol Psychother 2000;**29**:117–126.
42. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 1997;**36**:340–348.
43. Wingenfeld K, Spitzer C, Mensebach C et al. The German version of the Childhood Trauma Questionnaire, CTQ: preliminary psychometric properties. Psychother Psychosom Med Psychol 2010;**60**:442–450.
44. Walker EA, Newman E, Koss M, Bernstein D. Does the study of victimization revictimize the victims? Gen Hosp Psychiatry 1997;**19**:403–410.
45. Goodman WK, Price LH, Rasmussen SA et al. The Yale-Brown Obsessive Compulsive Scale: II validity. Arch Gen Psychiatry 1989;**46**:1012–1016.
46. Hand I, Büttner-Westphal H. Die Yale-Brown Obsessive Compulsive Scale, Y-BOCS: Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen. Verhaltenstherapie 1991;**1**:223–225.
47. Foa EB, Huppert JD, Leiberg S. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess 2002;**14**:485–496.
48. Gönner S, Leonhart R, Ecker W. The obsessive-compulsive inventory-revised, OCI-R: validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. J Anxiety Disord 2008;**22**:734–749.
49. Steer RA, Ball R, Ranieri WF, Beck AT. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. Psychol Rep 1997;**80**:443–446.
50. Hautzinger M, Keller F, Kühner C. Beck Depressions-Inventar, BDI-II. Frankfurt: Harcourt Test Services, 2006.
51. Baer L. Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. J Clin Psychiatry 1994;**55**:18–23.
52. Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF. Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am J Psychiatry 2008;**165**:1532–1542.
53. Glahn DC, Knowles EE, McKay DR et al. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. Am J Med Genet B Neuropsychiatr Genet 2014;**165**:122–130.
54. Leboyer M, Leboyer M, Bellivier F et al. Psychiatric genetics: search for phenotypes. Trends Neurosci 1998;**21**:102–105.
55. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;**160**:636–645.
56. Faravelli C, Sauro CL, Godini L et al. Childhood stressful events, HPA axis and anxiety disorders. World J Psychiatry 2012;**2**:13–25.
57. Nemeroff CB. Neurobiological consequences of childhood trauma. J Clin Psychiatry 2004;**65**(Suppl. 1):18–28.
58. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci 2005;**7**:103–123.
59. Heim C, Newport DJ, Heit S et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000;**284**:592–597.
60. De Carvalho HW, Pereira R, Frozi J, Bisol LW, Ottoni GL, Lara DR. Childhood trauma is associated with maladaptive personality traits. Child Abuse Negl 2015;**44**:18–25.
61. Tyrka AR, Wier LM, Price LH et al. Cortisol and ACTH responses to the Dex/CRH test: influence of temperament. Horm Behav 2008;**53**:518–525.
62. Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr Scand 2014;**129**:180–192.
63. Lim L, Radua J, Rubia K. Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. Am J Psychiatry 2014;**171**:854–863.
64. Brooks SJ, Naidoo V, Roos A, Fouché JP, Lochner C, Stein DJ. Early-life adversity and orbitofrontal and cerebellar volumes in adults with obsessive-compulsive disorder: voxel-based morphometry study. Br J Psychiatry 2016;**208**:34–41.
65. Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later

psychopathology: evidence from rodent and primate models. Dev Psychopathol 2001;**13**:419–449.
66. Tsuang MT, Bar JL, Stone WS, Faraone SV. Gene-environment interactions in mental disorders. World Psychiatry 2004;**3**:73–83.
67. Spinhoven P, Elzinga BM, Van Hemert AM, De Rooij M, Penninx BW. Childhood maltreatment, maladaptive personality types and level and course of psychological distress: a six-year longitudinal study. J Affect Disord 2016;**191**:100–108.
68. Li X, Wang Z, Hou Y, Wang Y, Liu J, Wang C. Effects of childhood trauma on personality in a sample of Chinese adolescents. Child Abuse Negl 2014;**38**:788–796.
69. Lennertz L, Grabe HJ, Ruhrmann S et al. Perceived parental rearing in subjects with obsessive-compulsive disorder and their siblings. Acta Psychiatr Scand 2010;**121**:280–288.
70. Stewart SE, Rosario MC, Baer L et al. Four-factor structure of obsessive-compulsive disorder symptoms in children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2008;**47**:763–772.
71. Leopold R, Backenstrass M. Neuropsychological differences between obsessive-compulsive washers and checkers: a systematic review and meta-analysis. J Anxiety Disord 2015;**30**:48–58.
72. Van Den Heuvel OA, Remijnse PL, Mataix-Cols D et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain 2009;**132**:853–868.
73. Fergusson DM, Mullen PE. Childhood sexual abuse: an evidence based perspective. Thousand Oaks, CA: Sage, 1999.
74. MacDonald K, Thomas ML, Sciolla AF et al. Minimization of childhood maltreatment is common and consequential: results from a large, multinational sample using the childhood trauma questionnaire. PLoS ONE 2016;**11**:e0146058.
75. Wilhelm K, Niven H, Parker G, Hadzi-Pavlovic D. The stability of Parental Bonding Instrument over a 20-year period. Psychol Med 2005;**35**:387–393.
76. Brewin CR, Andrews B, Gotlib IH. Psychopathology and early experience: a reappraisal of retrospective reports. Psychol Bull 1993;**113**:82–98.
77. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: a meta-analysis of published literature childhood trauma and adult depression. Eur Psychiatry 2015;**30**:665–680.
78. Cougle JR, Timpano KR, Sachs-Ericsson N, Keough ME, Riccardi CJ. Examining the unique relationships between anxiety disorders and childhood physical and sexual abuse in the National Comorbidity Survey-Replication. Psychiatry Res 2010;**177**:150–155.
79. Luciano M, Huffman JE, Arias-Vásquez A et al. Genome-wide association uncovers shared genetic effects among personality traits and mood states. Am J Med Genet B Neuropsychiatr Genet 2012;**159**:684–695.
80. Okbay A, Baselmans BM, De Neve JE et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 2016;**48**:624–633.
81. Middeldorp CM, De Moor MHM, McGrath LM et al. The genetic association between personality and major depression or bipolar disorder A polygenic score analysis using genome-wide association data. Transl Psychiatry 2011;**1**:e50.
82. Kandemir H, Erdal ME, Selek S et al. Microribonucleic acid dysregulations in children and adolescents with obsessive-compulsive disorder. Neuropsychiatr Dis Treat 2015;**11**:1695–1701.
83. Yue W, Cheng W, Liu Z et al. Genome-wide DNA methylation analysis in obsessive-compulsive disorder patients. Sci Rep 2016;**6**:31333.
84. Nissen JB, Skarphedinsson G, Weidle B et al. Familial occurrence of tic disorder, anxiety and depression is associated with the clinical presentation of obsessive compulsive disorder, OCD in children and adolescents. J Obsessive Compuls Relat Disord 2016;**9**:59–65.
85. Houtepen LC, Vinkers CH, Carrillo-Roa T et al. Genome-wide DNA methylation levels and altered cortisol stress reactivity following childhood trauma in humans. Nat Commun 2016;**7**:10967.

Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Analyses with age and gender as covariates.

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ORIGINAL ARTICLE

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Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives

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Abstract

Recent evidence indicates that patients with obsessive-compulsive disorder (OCD) as well as their unaffected first-degree relatives show deficits in the volitional control of saccades, suggesting that volitional saccade performance may constitute an endophenotype of OCD. Here, we aimed to replicate and extend these findings in a large, independent sample. One hundred and fifteen patients with OCD, 103 healthy comparison subjects without a family history of OCD, and 31 unaffected first-degree relatives of OCD patients were examined using structured clinical interviews and performed a volitional saccade task as well as a prosaccade task. In contrast to previous reports, neither patients nor relatives showed impairments in the performance of volitional saccades compared to healthy controls. Notably, medicated patients did not differ from nonmedicated patients, and there was no effect of depressive comorbidity. Additional analyses investigating correlations between saccade performance and OCD symptom dimensions yielded no significant associations. In conclusion, the present results do not support the notion that volitional saccade execution constitutes an endophenotype of OCD. Possible explanations for inconsistencies with previous studies are discussed.

KEYWORDS

endophenotype, obsessive-compulsive disorder, OCD, unaffected relatives, volitional saccades

1 Introduction

Obsessive-compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors), which affects 1–3% of the population worldwide (Weissman et al., 1994). Across patients, obsessive-compulsive symptoms are highly heterogeneous, covering dimensions of washing/contamination, ordering/symmetry, forbidden thoughts, and hoarding (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman 2008). Mounting evidence from family studies indicates that OCD is familial, with first-degree relatives having a fivefold increased risk on average to also be affected with the disease (Grabe et al., 2006; Nestad et al., 2000;

Pauls, Alsobrook, Goodman, Rasmussen, & Leckmann, 1995). Twin studies of OCD and OCD-related traits yield heritability estimates around 50% (Nicolini, Arnold, Nestadt, Lanzagorta, & Kennedy, 2009; van Grootheest et al., 2008). However, the identification of specific genetic variants underlying this heritability proved to be difficult, with two large genome-wide association studies lacking genome-wide significant hits (Mattheisen et al., 2015; Stewart et al., 2013). To address this issue, research has recently turned to endophenotypes as potential vulnerability factors of OCD, which are quantitative variables (e.g., cognitive or neurophysiological) associated with the disease while being distinct from the clinical phenotype itself (Gottesmann & Gould, 2003). Endophenotypes are supposed to depend upon variation in fewer genes than the more complex disease phenotype and are therefore assumed to be more tractable to genetic analysis. Within families, endophenotypes and the disorder cosegregate, so that unaffected relatives are expected to show abnormalities similar to those observed in patients. In line with this concept, several cognitive dysfunctions as well as neurophysiological aberrations found in OCD patients have also been observed in unaffected first-degree relatives, for example, deficits in performance monitoring (Riesel, Endrass, Kaufmann, & Kathmann, 2011) and response inhibition (Chamberlain et al., 2007; Menzies et al., 2007; Rajender et al., 2011).

Another promising candidate endophenotype of OCD is volitional control of behavior, which can be defined by contrasting it with stimulus-controlled responses: Stimulus-controlled responses depend on stimulation and are thus externally controlled, whereas volitional responses rely on arbitrary stimulus-response rules and are internally controlled (Haggard, 2008). In light of this, saccade tasks appear to be a fruitful method to examine volitional control of behavior, as they allow contrasting saccades that are elicited by the sudden onset of a peripheral stimulus (prosaccades) with saccades that rely on internal stimulus-response representations, namely, antisaccades and simple volitional saccades. In the antisaccade task, subjects are required to look in the opposite direction of a peripherally appearing stimulus. Thus, the volitional response must be generated while inhibiting a stimulus-controlled response at the same time. In simple volitional saccades tasks, saccades are instructed by a centrally presented arbitrary cue, and thus only require volitional response generation.

OCD patients perform normally in prosaccade tasks in terms of error rates, latencies (for a review, see Jaafari et al., 2011), and intrasubject variability of latencies (Theleritis, Evdokimidis, & Smyrnis, 2014). Research using the antisaccade task provides more mixed results, with studies reporting increased (Agam et al., 2014; Damilou, Apostolakis, Thrapsanioti, Theleritis, & Smyrnis, 2016; Lennertz et al., 2012; Rosenberg, Dick, O'Hearn, & Sweeney, 1997; Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992) or normal (Maruff, Purcell, Tyler, Pantelis, & Currie, 1999; McDowell & Clementz, 1997; Spengler et al., 2006; van der Wee et al., 2006) error rates, and increased (Lennertz et al., 2012; Maruff et al., 1999; McDowell & Clementz, 1997; van der Wee et al., 2006) or normal (Agam et al., 2014; Damilou et al., 2016; Rosenberg et al., 1997; Spengler et al., 2006) latencies. The standard deviation (*SD*) of antisaccade latencies was also increased in one study (Damilou et al., 2016). One possible explanation for mixed results in the antisaccade task is that the generation of antisaccades is not independent from processing of the external stimulus, making it more sensitive toward stimulus parameters, and less volitionally controlled. Zhang and Barash (2000) recorded neuronal activity during an antisaccade task and found that the motor command for the antisaccade is directly influenced by the visual input of the peripheral stimulus. Furthermore, latencies for correct antisaccades are shorter than for simple volitional saccades, indicating a smaller degree of required volitional processing (Kloft, Kischkel, Kathmann, & Reuter, 2011; Kloft, Reuter, Viswanathan, Kathmann, & Barton, 2012). In light of this, simple volitional saccades seem more appropriate to examine volitional control of behavior in a precise manner. Given the involvement of fewer circumscribed cognitive functions in the control of volitional saccades and the extensive knowledge of the neural structures involved in their control (Bender et al., 2013; McDowell, Dyckman, Austin, & Clementz, 2008; Reuter, Kaufmann, Bender, Pinkpank, & Kathmann, 2010), the study of volitional saccades might help in specifying cognitive impairments, which in turn should aid in identifying the biological vulnerabilities of psychiatric disorders (Sonuga-Barke, 2010). Thus, simple volitional saccades seem to be a useful tool in endophenotype research.

There is growing evidence that OCD patients have impairments in responses that require internal guidance. Gillan et al. (2011) showed that volitional action control in OCD patients was reduced in an outcome devaluation task, and Gentsch, Schütz-Bosbach, Endrass, and Kathmann (2012) observed that OCD was associated with deficient internal motor predictions of actions. Importantly, in both studies, the

impairments were found in tasks that did not require a competing response. In the same line, impaired performance of OCD patients was found in tasks that required volitional saccade generation without parallel response inhibition (Kloft et al., 2011; Kloft, Reuter, Riesel, & Kathmann, 2013; Maruff et al., 1999). The same deficit was observed in a small sample of unaffected first-degree relatives of OCD patients, providing the first evidence for deficient volitional control of behavior as a candidate endophenotype for OCD (Kloft et al., 2013).

In the present study, we aimed to replicate and extend the findings reported by Kloft et al. (2013) in a large, independent sample. Besides saccade mean latencies, within-subject variability as well as the spatial accuracy of saccades may represent informative outcome measures (Damilou et al., 2016; Tien et al., 1992). Hence, *SD*s of latencies and mean saccade amplitudes were assessed, as well. Furthermore, since distinct OCD symptom dimensions are associated with differences in brain structure (van den Heuvel et al., 2009), brain response to symptom provocation (Mataix-Cols et al., 2004), and neuropsychological performance (Leopold & Backenstrass, 2015), we investigated whether the execution of volitional saccades varies across OCD symptom dimensions.

2 Methods

2.1 Participants

One hundred and fifteen patients with OCD, 103 healthy comparison subjects, and 31 unaffected first-degree relatives of OCD patients ($n = 16$ parents, $n = 14$ siblings, and $n = 1$ offspring) participated in the study. Patients and controls were matched for age, gender, and education. With regard to age, relatives were significantly older than patients and controls (see Table 1 for sample characteristics). OCD patients and relatives were recruited via the outpatient clinics at the Department of Psychology of Humboldt University Berlin and at the Department of Psychiatry and Psychotherapy of the University of Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements. A total of 160 subjects were assessed in Berlin ($n = 84$ OCD patients, $n = 16$ unaffected relatives, $n = 60$ control subjects), and 89 subjects were assessed in Bonn ($n = 31$ OCD patients, $n = 15$ unaffected relatives, $n = 43$ control subjects). Of the relatives, 20 were related to patients who participated in the present study, while the remaining 11 were not related to the patients assessed here. In order to validate these subjects' status as a relative

of an OCD patient, they were recruited via patients of the clinics who themselves did not meet the inclusion criteria of the study or did not consent to participate. Moreover, the family history screen (Weissmann et al., 2000) was applied. All participants were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV (SCID-I; First, Spitzer, Gibbon, & Williams, 1997; Wittchen, Zaudig, & Fydrich, 1997). To establish cross-site reliability of clinical ratings, all instructions were standardized, and raters completed assessments of four training videos. Patients and relatives were only included if they were (a) free of past or present psychotic, bipolar, or substance-related disorders, (b) did not take neuroleptic medication in the past 4 weeks, and (c) did not use benzodiazepines in the past 2 weeks. Additionally, healthy controls were excluded if they (a) took any psychoactive medication in the past 3 months, (b) had a current Axis I disorder, (c) lifetime diagnosis of OCD or tic disorder, or (d) a family history of OCD. All relatives were free of past or present OCD.

Fifty OCD patients were medicated, with $n = 46$ taking selective serotonin reuptake inhibitors (SSRIs) and $n = 16$ taking other antidepressants. Forty-four patients were medication naive. Furthermore, the majority of patients had one or more current comorbid Axis I disorder: major depression ($n = 27$ current episode, $n = 31$ remitted), dysthymia ($n = 8$), panic disorder without agoraphobia ($n = 2$), social phobia ($n = 9$), specific phobia ($n = 7$), generalized anxiety disorder ($n = 2$), posttraumatic stress disorder ($n = 2$), attention deficit/hyperactivity disorder ($n = 1$), anorexia nervosa ($n = 1$), binge eating disorder ($n = 3$), tic disorder ($n = 7$), skin picking disorder ($n = 7$), hypochondria ($n = 1$), body dysmorphic disorder ($n = 2$), hoarding disorder ($n = 1$), pain disorder ($n = 1$), and unspecific somatoform disorder ($n = 1$). Severity of OCD symptoms was assessed using the German versions of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al., 1989; Hand & Büttner-Westphal, 1991) and the Obsessive-Compulsive Inventory-Revised (OCI-R; Foa et al., 2002; Gönner, Leonhart, & Ecker, 2008). Symptom dimensions were measured via the Y-BOCS Symptom Checklist (Y-BOCS CL; Goodman et al., 1989). The Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979; Neumann & Schulte, 1989) and the Beck Depression Inventory-II (BDI-II; Hautzinger, Keller, & Kühner, 2006; Steer, Ball, Ranieri, & Beck, 1997) were used to assess the severity of current depressive symptoms. Handedness was measured with the Edinburgh Handedness Scale (Oldfield, 1971). All participants had normal or corrected-to-normal vision and were free of any neurological disease (lifetime).

Table 1. *Demographic and clinical characteristics of patients with OCD, unaffected first-degree relatives and healthy control subjects.*

	Patients with OCD	Unaffected first-degree relatives	Healthy control subjects	Statistic	*p*
N	115	31	103		
Mean age, years (*SD*)	32.87 (9.95)	43.97 (15.93)	34.54 (12.87)	$F(2,246) = 10.43$	< 0.001
Gender (% male)	39.1	32.3	36.1	$X^2(2) = 0.85$	0.65
Education (*SD*)[a]	4.81 (1.97)	4.60 (1.85)	5.23 (1.65)	$F(2,241) = 2.02$	0.14
Handedness (*SD*)[b]	34.89 (8.56)	36.35 (7.48)	35.04 (7.56)	$F(2,238) = 0.42$	0.66
Mean OCI-R score (*SD*)	26.45 (11.84)	7.13 (7.14)	4.92 (5.10)	$F(2,244) = 166.94$	< 0.001
Mean BDI-II score (*SD*)	19.22 (11.03)	7.03 (8.04)	2.82 (4.56)	$F(2,244) = 103.64$	< 0.001
Mean Y-BOCS score (*SD*)[c]	22.46 (6.00)				
Mean MADRS score (*SD*)[c]	12.99 (9.34)				
Mean age of onset (*SD*)[c]	20.85 (11.84)				

Note. BDI-II, Beck Depression Inventory-II; MADRS, Montgomery Asberg Depression Rating Scale; OCD, obsessive-compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; *SD*, Standard Deviation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] Education was assessed on a scale from 1 to 7.

[b] Handedness was measured using the Edinburgh Handedness Scale (0 = maximal left-handedness; 40 = maximal right-handedness).

[c] Y-BOCS, MADRS, and age of onset were only assessed in patients.

Written informed consent was obtained, and participants were compensated for their time. The study was in accordance with the revised Declaration of Helsinki, and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Clinic Bonn.

2.2 Eye movement recordings

Testing took place in a quiet, dimly lit room. Participants were seated comfortably in front of a 22-inch LCD monitor (Viewsonic; height: 29.5 cm; width: 47.5 cm; resolution: 1,680 × 1,050 pixels; 60 Hz refresh rate) with a distance from eyes to screen of 70 cm. A chin rest was used to minimize head movements. At the Bonn assessment site, movements of the right eye were recorded using the EyeLink 1000

system (SR Research, Ltd., Mississauga, ON, Canada) at a sampling frequency of 1000 Hz, while in Berlin, eye movements were recorded using the EyeLink II system (SR Research) at a sampling rate of 250 Hz. Before the task started, the eye-tracker was calibrated with a five-point calibration task (0°, horizontal ± 13.3°, vertical ± 9.3°). Immediately before the experimental sessions, participants received 10 practice trials during which the tester ensured that the participant had understood the instructions. As a comparison condition for the volitional saccade task, all participants completed a prosaccade task beforehand (including five practice trials).

2.3 Saccadic tasks

Saccadic tasks were programmed using SR Research's Experiment Builder (version 1.10.1241). The volitional saccade task (Figure 1a) comprised 60 trials, which were presented in one block lasting for 1.5 min. In each trial, participants had to fixate a central diamond-shaped stimulus (width and height 0.46°) with an arrowhead pointing to the left and the right. With a variable latency interval of 1,000–2,000 ms, one of the two marginal lines surrounding the stimulus vanished, leaving an arrow pointing in one direction (go signal). Participants were required to look to the side indicated by the arrow as fast as possible. Saccades were thus guided by the internal representation of the stimulus-response relation.

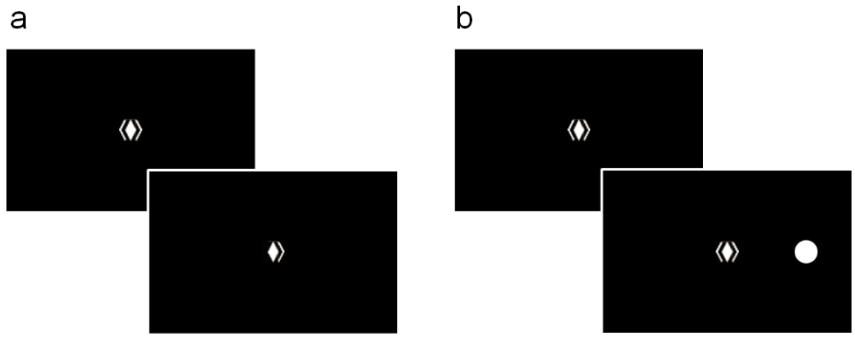

Figure 1. (a) Volitional saccade task. **(b)** Prosaccade task. In both trials presented, subjects had to perform a rightward saccade. Stimulus sizes are enlarged for better visibility.

In the prosaccade task (Figure 1b), the same diamond-shaped fixation stimulus was used to ensure comparability between tasks. With a variable interval of 1,000–2,000 ms, a target stimulus (width and height 0.46°) appeared in either the left or the right periphery at an angle of 16°, to which subjects were instructed to direct their gaze

as quickly and accurately as possible. Similar to the volitional saccade task, the central stimulus remained on screen throughout each of the 60 trials. However, the marginal lines surrounding the central stimulus did not change. Responses were thus only guided externally by the peripheral target.

Task design parameters were similar to those employed by Kloft et al. (2013), though the number of trials was increased to 60, in order to improve reliability. In previous research, group differences of comparable effect sizes were observed in a blocked task design (Kloft et al., 2011) as well as in a randomized design (Kloft et al., 2013). Here, we used a blocked design, since a randomized task design may elicit stronger demands on other cognitive domains such as task switching in addition to mere volitional saccade control. Volitional saccade and prosaccade blocks were presented in a fixed order, as the strong main effect of task (latency of volitional saccades > prosaccades) is well established throughout the literature (Kloft et al., 2011, 2013; Maruff et al., 1999; Reuter et al., 2011).

Tasks were part of a larger oculomotor battery with additional tasks, whose results will be reported elsewhere. Completion of the whole battery took approximately 15 min.

2.4 Eye movement analysis

Saccades were identified using SR Research's saccade detection algorithm (Data Viewer, version 1.11.900) and individually verified by a rater. Criteria for the identification of saccades were a velocity > 30°/s, an acceleration > 8000°/s^2, a minimum amplitude of 1°, and a minimum latency to the arrow stimulus of 80 ms. Trials containing anticipatory saccades or blinks within the time window from 100 ms before until 80 ms after the go signal were excluded. Furthermore, trials were discarded if the gaze position at saccade onset deviated more than 2.3° (100 pixels) from the fixation stimulus position. Three subjects, who performed fewer than 15 valid trials in either of the tasks, were excluded from the analyses ($n = 1$ patient, $n = 1$ relative, and $n = 1$ control; Wöstmann et al., 2013). For each subject, mean latencies and *SD*s as well as mean amplitudes of correctly performed volitional saccades and prosaccades were calculated.

2.5 Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Release 23.0 (SPSS Inc., Chicago, IL). Main effects of task and age were investigated across the entire sample. To test the hypothesis of impaired volitional control in OCD patients, we first conducted a 2 × 2 analysis of variance (ANOVA) with group as between-subjects factor (OCD patients vs. healthy comparison subjects) and task (prosaccades vs. volitional saccades) as within-subject factor. Secondly, since relatives were significantly older than OCD patients and healthy volunteers, we investigated a subsample of 31 OCD patients, 31 relatives, and 31 healthy comparison subjects matched for age, gender, and education, in order to test for performance differences between the three groups. Distinct ANOVAs were performed with mean saccade latency, *SD* of latencies, and mean saccade amplitude as dependent variables.

Associations with specific OCD symptom dimensions were investigated using the Y-BOCS CL. Following the procedure established in previous studies (Baer, 1994; Bloch et al., 2008), the 13 main categories of the Y-BOCS CL were coded as 1 if the patient reported having experienced at least one symptom of the respective category. Otherwise, the category was coded as 0. These binary variables were then fed into an exploratory principal component analysis (PCA) with varimax rotation. Factors were extracted based on the Kaiser-Guttmann criterion (i.e., eigenvalue > 1). For each OCD patient, factor scores were exported to use in further analyses.

Pearson's correlation coefficients were computed in order to explore relationships between mean saccade latencies and *SD*s, mean amplitudes, and continuous clinical variables. Group differences in demographic and clinical characteristics were tested using ANOVAs, and Fisher's chi-square test was used to compare sex ratios across groups. We also performed exploratory ANOVAs using medication (any psychoactive medication within the past 4 weeks ($n = 50$) vs. no psychoactive medication within the past 4 weeks ($n = 63$)) and depressive comorbidity (lifetime diagnosis of major depression ($n = 58$) vs. no lifetime diagnosis of major depression ($n = 57$)) as between-subjects factor in OCD patients. The alpha level was set at 0.05 for all statistical analyses.

3 Results

3.1 Clinical characteristics

Groups differed significantly regarding OCI-R, $F(2, 244) = 166.94$, $p < .001$, and BDI-II, $F(2, 244) = 103.64$, $p < .001$. Post hoc contrasts (Tukey's HSD) revealed that OCD patients reported significantly higher OCI-R scores than unaffected relatives and healthy volunteers (both ps $< .001$), while there was no difference between relatives and controls ($p = .46$). With respect to depressive symptoms, OCD patients showed significantly higher BDI-II scores than both of the other groups (both ps $< .001$). Yet, relatives also exhibited elevated scores compared to controls ($p = .043$).

3.2 Saccade performance across groups

Mean saccade latencies were significantly faster in the prosaccade task than in the volitional saccade task, $F(1, 247) = 50.15$, $p < .001$. A main effect of age indicated that saccade latencies increased with age over all subjects, $F(1, 247) = 81.89$, $p < .001$. Furthermore, there was a significant interaction between age and saccade task, indicating that the difference between volitional saccades and prosaccades increased with age, $F(1, 247) = 22.82$, $p < .001$. Likewise, analyses of saccade latency *SD*s revealed a main effect of task type, $F(1, 247) = 39.75$, $p < .001$, with smaller *SD*s in the prosaccade task than in the volitional saccade task. A main effect of age indicated that *SD*s of saccade latencies increased with age across all subjects, $F(1, 247) = 16.13$, $p < .001$. The Age × Task interaction also reached significance, $F(1, 247) = 3.77$, $p = .049$. Saccade amplitudes did not differ between prosaccade and volitional saccade tasks, $F(1, 247) = 0.19$, $p = .89$. There was neither a significant main effect of age, $F(1, 247) = 0.42$, $p = .52$, nor a significant Task × Age interaction, $F(1, 247) = 0.63$, $p = .43$.

Importantly, there was also no effect of study site on saccade performance, $F(1, 246) = 0.04$, $p = .84$ for mean latencies, $F(1, 246) = 1.86$, $p = .17$ for *SD*s, and $F(1, 246) = 0.37$, $p = .54$ for amplitudes. Age was included as a covariate in these analyses, as subjects recruited in Bonn were significantly older than the subjects recruited in Berlin, $t(139.15) = -3.60$, $p < .001$.

3.3 Saccade performance in OCD patients and healthy comparison subjects

Comparing saccade latencies between OCD patients and healthy controls neither yielded a main effect of group, $F(1, 216) = 0.59$, $p = .45$, nor a significant

interaction of group and task type, $F(1, 216) = 0.72$, $p = .40$ (see Figure 2). Similarly, there were no significant effects of group, $F(1, 216) = 0.005$, $p = .95$ and $F(1, 216) = 1.11$, $p = .29$, respectively, and Group × Task interaction, $F(1, 216) = 0.66$, $p = .42$ and $F(1, 216) = 0.85$, $p = .36$, respectively, with regard to saccade latency *SD*s and amplitudes.

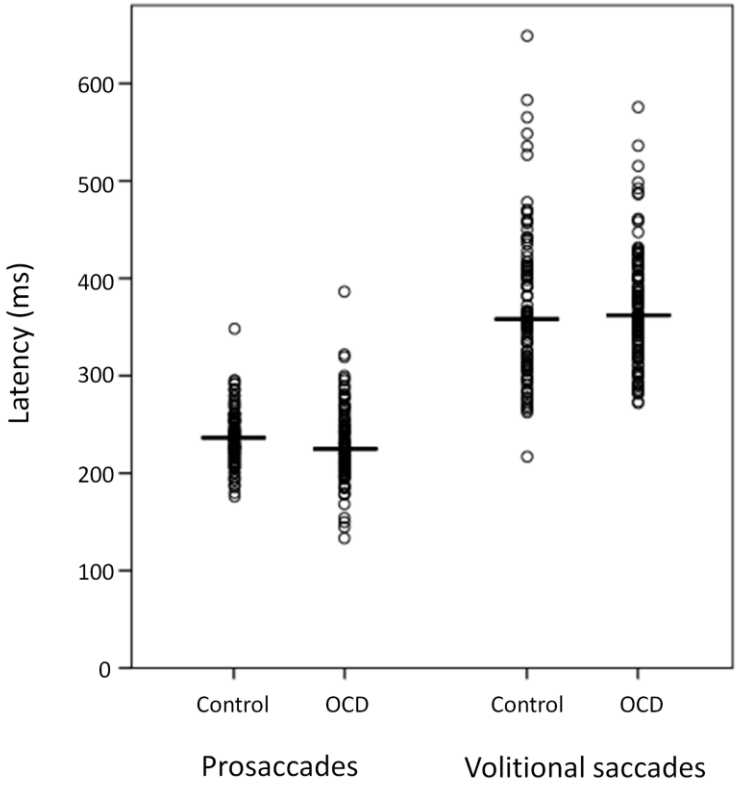

Figure 2. Latencies of prosaccades and volitional saccades in patients with obsessive-compulsive disorder (OCD) and matched health control subjects. Bars indicate mean values.

Excluding patients with any current comorbid Axis I disorder yielded similarly insignificant results.

3.4 Saccade performance in OCD patients, unaffected relatives, and healthy comparison subjects

Given the substantial influence of age on saccade latencies and *SD*s, performance differences between OCD patients, relatives, and healthy comparison subjects were investigated in a subsample matched for age, gender, and education. Again, neither of the ANOVAs yielded a significant effect of group, $F(2, 90) = 0.16$, $p = .85$ for latencies, $F(2, 90) = 1.04$, $p = .36$ for *SD*s, and $F(2, 90) = 1.53$, $p = .22$ for

amplitudes, or Group × Task interaction, $F(2, 90) = 0.25$, $p = .78$ for latencies, $F(2, 90) = 0.01$, $p = .99$ for *SD*s, and $F(2, 90) = 1.42$, $p = .25$ for amplitudes.

3.5 Effects of medication, depressive comorbidity, and OCD severity

To investigate potential effects of medication, we compared medicated and unmedicated OCD patients with regard to the three saccade parameters. There was neither a significant effect of medication status nor of the Medication Status × Task interaction on mean saccade latencies, $F(1, 111) = 0.29$, $p = .59$ and $F(1, 111) = 0.03$, $p = .86$, respectively; latency *SD*s, $F(1, 111) = 0.31$, $p = .58$ and $F(1, 111) = 0.83$, $p = .36$, respectively; and mean amplitudes, $F(1, 111) = 0.08$, $p = .77$ and $F(1, 111) = 0.24$, $p = .62$, respectively, indicating that current psychoactive medication did not affect the performance of OCD patients.

Moreover, we did not observe any main or interaction effects of depressive comorbidity on either mean latencies, $F(1,113) = 0.09$, $p = .77$ and $F(1, 113) = 0.54$, $p = .47$, respectively; SDs of latencies, $F(1, 113) = 0.39$, $p = .53$ and $F(1, 113) = 0.01$, $p = .93$, respectively; or mean amplitudes, $F(1, 113) = 0.57$, $p = .45$ and $F(1, 113) = 0.001$, $p = .97$, respectively.

Neither of the saccade parameters was significantly correlated with Y-BOCS scores (all $|r| < .12$, $p > .05$).

3.6 Symptom dimensions

PCA yielded five factors representing the dimensions checking/taboo thoughts, washing/contamination, counting/repeating, ordering/symmetry, and hoarding. Together, these factors explained 65.17% of variance in OCD symptoms. None of the factor scores was significantly correlated with mean saccade latencies, *SD*s, and amplitudes in either of the tasks (all $|r| < 0.18$, $p > .05$).

3.7 Laterality effects

We investigated whether there were any laterality asymmetries in mean saccade latencies, latency *SD*s, and saccade amplitudes, by including the target direction as a third factor in the ANOVAs. Only right-handed subjects were considered for these analyses (Edinburgh handedness score ≥ 27), as handedness has been shown to affect left-right asymmetries in saccade parameters (Hutton & Palet, 1986; Pirozzolo & Rayner, 1980). With regard to saccade latencies, the comparison of OCD

patients ($n = 101$) and healthy controls ($n = 93$) yielded no significant effects of direction, $F(1, 192) = 1.42$, $p = .24$; group, $F(1, 192) = 0.20$, $p = .66$; Task × Direction, $F(1, 192) = 2.12$, $p = .15$; and Group × Direction, $F(1, 192) = 2.76$, $p = .10$. Likewise, no significant effects of direction, $F(1, 192) = 0.84$, $p = .36$; group, $F(1, 192) = 0.64$, $p = .42$; Task × Direction, $F(1, 192) = 0.13$, $p = .72$; and Group × Direction, $F(1, 192) = 0.09$, $p = .77$, were observed on latency *SD*s. Regarding saccade amplitudes, there were strong effects of direction, $F(1, 192) = 13.10$, $p < .001$, and the Task × Direction interaction, $F(1, 192) = 6.93$, $p = .009$, indicating that amplitudes to the right were larger than amplitudes to the left, especially in the volitional saccade task. This bias occurred similarly in both patients and controls, as there were no significant effects of group, $F(1, 192) = 1.53$, $p = .22$, and Group × Direction, $F(1, 192) = 1.23$, $p = .27$. Similar results were obtained in the matched subsample of OCD patients, unaffected relatives, and healthy comparison subjects.

4 Discussion

By assessing the execution of volitional saccades in OCD patients, unaffected first-degree relatives, and healthy volunteers, the present study sought to investigate whether volitional control of behavior constitutes a promising endophenotype of OCD. In line with previous studies, latencies and within-subject variability of latencies in the prosaccade task, which served as a control task of basic oculomotor function, were intact in patients and first-degree relatives (Jaafari et al., 2011; Kloft et al., 2013). In contrast to previous reports (Kloft et al., 2011, 2013), neither patients nor relatives showed impairments in the performance of volitional saccades compared to healthy controls. There was no difference regarding within-subject variability of volitional saccade latencies, and the examination of mean amplitudes of prosaccades and volitional saccades did not yield any differences between the three groups.

Several factors may contribute to inconsistent findings across studies. First, OCD is a clinically heterogeneous disorder with different subgroups being differentially impaired in cognitive functioning. Most notably, patients with symptoms in the domain of checking and doubting show significantly worse task performance across various cognitive domains than patients with washing and cleaning compulsions (Leopold & Backenstrass, 2015). Symptom heterogeneity across samples may thus account for divergent findings. In order to investigate the influence of OCD symptom dimensions on task performance, we conducted a PCA over an extensive list of OCD symptoms

and correlated the resulting five factor scores with the oculomotor response measures. On the whole, these factors are in accordance with previous reports (Bloch et al., 2008). However, as we did not observe any significant correlation between symptom dimension scores and task performance, the lack of association between OCD and volitional saccade execution is unlikely to be explained by variation in OCD symptoms across studies.

Second, the inconsistent results may be accounted for by differences in task design. In the study of Kloft et al. (2013), three different saccade tasks, that is, cued volitional saccades, uncued volitional saccades, and free choice saccades, were presented pseudorandomly interleaved within one block. Accordingly, subjects had to keep in mind the different task sets, select their response based on the presented cue stimulus, and then execute the saccade. Considering this, it becomes apparent that additional demands on cognitive flexibility may substantially contribute to task performance. This assumption is in line with the observation that response latencies were substantially longer in the interleaved task design (Kloft et al., 2013) than in the present study's blocked design. Previous research has shown that, compared to healthy controls, OCD patients as well as their first-degree relatives exhibit deficits in set shifting and cognitive flexibility, as assessed by the Wisconsin Card Sorting Test (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Rajender et al., 2011), the Intradimensional/Extradimensional Shift task (Chamberlain et al., 2007), or a reversal learning task (Chamberlain et al., 2008). The effect of impaired volitional saccade execution in the interleaved task may hence partially depend on the demands on cognitive flexibility. Still, enhanced latencies of volitional saccades have also been observed in OCD patients compared to healthy volunteers when a blocked design was used (Kloft et al., 2011). Thus, inconsistencies cannot be accounted for by task design alone.

In line with general findings from oculomotor research (Munoz, Broughton, Goldring, & Armstrong 1998), our results indicate that response latencies in the volitional saccade task are strongly dependent on the subjects' age. With an effect size of $\eta^2 = .23$, age's impact vastly exceeds the small- to medium-sized effect of OCD reported by Kloft et al. (2013; $\eta^2 = .09$), emphasizing the importance of controlling for age differences across groups. An apparent limitation of the present study is that relatives were significantly older than patients and controls. However, analyses were run in a subsample matched for age, gender, and education, and comparing healthy

volunteers to OCD patients alone in the full sample did not yield any significant group differences.

Furthermore, the lack of replication cannot be accounted for by lack of statistical power, as the groups of patients and controls were five times larger in the present investigation than in the previous study (Kloft et al, 2013; $n = 22$ for each of the three groups), and the sample of relatives was approximately 50% larger. Power analyses using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that there was a power of > 99% to detect effects of the same sizes as reported by Kloft et al. (2011, 2013). Alongside the large sample size, notable strengths of the present study include the thorough clinical characterization of subjects as well as the consideration of several covariates and moderating variables, such as symptom dimensions, medication, comorbidity, and age.

Evidence from studies investigating habits and goal-directed behavior indicates that patients with OCD have deficits in goal-directed action control (Gillan et al., 2011; Gillan & Robbins, 2014). However, whereas Gillan and colleagues used tasks relying on associative action-outcome learning to study these behaviors, patients in the present study performed behavior relying on instructed stimulus-response mappings. Future research may address the question whether this difference represents a critical factor with regard to behavioral control in OCD.

With respect to within-subject variability of saccadic latencies, our study might contribute to the question of diagnostic specificity of oculomotor dysfunctions. In schizophrenia patients, a similar pattern of results emerges in terms of saccade latencies: Prosaccade latencies are considered unaffected (Gooding & Basso, 2008), whereas most (e.g., Bender et al., 2013; Reuter, Elsner, Möllers, & Kathmann, 2016; Reuter, Jäger, Bottlender, & Kathmann, 2007) but not all (Reuter et al., 2011) studies on simple volitional saccade latencies found increased latencies. Looking at within-subject variability of saccade latencies, a different pattern appears. *SD*s of prosaccades and voluntary saccades are both increased in schizophrenia patients (Karantinos et al., 2014; Theleritis et al., 2014), whereas they are intact in the present and a prior OCD study (Theleritis et al., 2014). Thus, the distribution of saccade latencies seems to dissociate the two disorders and should be considered an important parameter in future saccade research of psychiatric disorders.

To our knowledge, this is the first study to explore saccadic laterality asymmetries in OCD patients and unaffected first-degree relatives. In line with

previous research in subjects from the general population (Beydagi, Yilmaz, & Süer 1999; Constantinidis et al., 2003; De Clerk, Crevits, & Van Maele, 2000; Honda, 2002; Vergilino-Perez et al., 2012), we did not observe any significant differences between the left and right visual fields regarding saccade latencies and latency *SD*s across the three participant groups. However, we found a strong directional asymmetry in saccade amplitudes, with amplitudes to the right being significantly larger than amplitudes to the left, especially in the volitional saccade task. Previous studies addressing laterality effects in saccade amplitudes are rather scarce and inconclusive. For example, Tien et al. (1992) did not find a directional bias in prosaccade amplitudes, whereas Vergilino-Perez et al. (2012) reported that rightward saccades were significantly larger than leftward saccades for healthy right-handed subjects with a dominant right eye. As our analyses on laterality effects were restricted to right-handed participants of whom the majority was right-eye dominant, the observation of Vergilino-Perez and colleagues is in line with the left-right asymmetry observed in the present study. Aside from the lacking directionality bias in the study of Tien et al., there were no differences between OCD patients and healthy comparison subjects regarding laterality effects, which is in accordance with our findings. Still, more research is clearly warranted to address the question of directional asymmetries in the general population as well as in psychiatric patients.

In conclusion, our results do not support the notion that volitional saccade execution constitutes an endophenotype of OCD. Medication status, comorbidity, and OCD symptom dimensions were not associated with oculomotor performance and thus do not account for inconsistencies with previous research.

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References

Agam, Y., Greenberg, J. L., Isom, M., Falkenstein, M. J., Jenike, E., Wilhelm, S., & Manoach, D. S. (2014). Aberrant error processing in relation to symptom severity in obsessive–compulsive disorder: A multimodal neuroimaging study. *NeuroImage: Clinical, 5*, 141–151. doi:10.1016/j.nicl.2014.06.002

Baer, L (1994). Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. Journal of Clinical Psychiatry, 55, 18–23. Bender, J., Reuter, B., Möllers, D., Kaufmann, C., Gallinat, J., & Kathmann, N. (2013). Neural correlates of impaired volitional action control in schizophrenia patients. *Psychophysiology, 50*(9), 872–884. doi:10.1111/psyp.12060

Beydagi, H., Yilmaz, A., & Süer, C. (1999). The effect of direction on saccadic eye movement parameters. *Journal of Basic and Clinical Physiology and Pharmacology, 10*(1), 73–77. doi:10.1515/JBCPP.1999.10.1.73

Bloch, M. H., Landeros-Weisenberger, A., Rosario, M. C., Pittenger, C., & Leckman, J. F. (2008). Meta-analysis of the symptom structure of obsessive-compulsive disorder. *American Journal of Psychiatry, 165*(12), 1532–1542. doi:10.1176/appi.ajp.2008.08020320

Cavedini, P., Zorzi, C., Piccinni, M., Cavallini, M. C., & Bellodi, L. (2010). Executive dysfunctions in obsessive-compulsive patients and unaffected relatives: Searching for a new intermediate phenotype. *Biological Psychiatry, 67*(12), 1178–1184. doi:10.1016/j.biopsych.2010.02.012

Chamberlain, S. R., Fineberg, N. A., Menzies, L. A., Blackwell, A. D., Bullmore, E. T., Chir, B., ... Sahakian, B. J. (2007). Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *American Journal of Psychiatry, 164*(2), 335–338. doi:10.1176/appi.ajp.164.2.335

Chamberlain, S. R., Menzies, L., Hampshire, A., Suckling, J., Fineberg, N. A., del Campo, N., ... Robbins, T. W. (2008). Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science, 321*(5887), 421–422. doi:10.1126/science.1154433

Constantinidis, T. S., Smyrnis, N., Evdokimidis, I., Stefanis, N. C., Avramopoulos, D., Giouzelis, I., & Stefanis, C. N. (2003). Effects of direction on saccadic performance in relation to lateral preferences. *Experimental Brain Research, 150*(4), 443–448. doi:10.1007/s00221-003-1454-0

Damilou, A., Apostolakis, S., Thrapsanioti, E., Theleritis, C., & Smyrnis, N. (2016). Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. *Psychophysiology, 53*(6), 796–805. doi:10.1111/psyp.12630

De Clerck, M., Crevits, L., & Van Maele, G. (2000). Saccades: Is there a difference between right and left? *Neuro-Ophthalmology, 24*(2), 327–330. doi:10.1076/noph.24.2.327.7157

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175–191. doi:10.3758/BF03193146

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *User's guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician version*. Arlington, VA: American Psychiatric Association Publishing.

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment, 14*(4), 485–496. doi:10.1037/1040-3590.14.4.485

Gentsch, A., Schütz-Bosbach, S., Endrass, T., & Kathmann, N. (2012). Dysfunctional forward model mechanisms and aberrant sense of agency in obsessive-compulsive disorder. *Biological Psychiatry, 71*(7), 652–659. doi:10.3389/fnhum.2014.00608

Gillan, C. M., Papmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., & de Wit, S. (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *American Journal of Psychiatry, 168*(7), 718–726. doi:10.1176/appi.ajp.2011.10071062

Gillan, C. M., & Robbins, T. W. (2014). Goal-directed learning and obsessive–compulsive disorder. *Philosophical Transactions of the Royal Society B, 369*(1655), 20130475. doi:10.1098/rstb.2013.0475

Gönner, S., Leonhart, R., & Ecker, W. (2008). The Obsessive–Compulsive Inventory-Revised (OCI-R): Validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. *Journal of Anxiety Disorders, 22*(4), 734–749. doi:10.1016/j.janxdis.2007.07.007

Gooding, D. C., & Basso, M. A. (2008). The tell-tale tasks: A review of saccadic research in psychiatric patient populations. *Brain and Cognition, 68*(3), 371–390. doi:10.1016/j.bandc.2008.08.024

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale: II. Validity. *Archives of General Psychiatry, 46*(11), 1012–1016. doi:10.1001/archpsyc.1989.01810110054008

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645. doi:10.1176/appi.ajp.160.4.636

Grabe, H. J., Ruhrmann, S., Ettelt, S., Buhtz, F., Hochrein, A., Schulze-Rauschenbach, S., ... Freyberger, H. J. (2006). Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. *American Journal of Psychiatry, 163*(11), 1986–1992. doi:10.1176/ajp.2006.163.11.1986

Haggard, P. (2008). Human volition: Towards a neuroscience of will. *Nature Reviews Neuroscience, 9*(12), 934–946. doi:10.1038/nrn2497

Hand, I., & Büttner-Westphal, H. (1991). Die Yale-Brown Obsessive Compulsive Scale (Y-BOCS): Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen. [The Yale-Brown Obsessive Compulsive Scale: A semistructured interview to assess the severity of obsessions and compulsions]. *Verhaltenstherapie, 1*(3), 223–225.

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II) [Beck Depression Inventory (BDI-II)]*. Frankfurt, Germany: Harcourt Test Services.

Honda, H. (2002). Idiosyncratic left-right asymmetries of saccadic latencies: Examination in a gap paradigm. *Vision Research, 42*(11), 1437–1445. doi:10.1016/S0042-6989(02)00050-0

Hutton, J. T., & Palet, J. (1986). Lateral saccadic latencies and handedness. *Neuropsychologia, 24*(3), 449–451. doi:10.1016/0028-3932(86)90033-3

Jaafari, N., Rigalleau, F., Rachid, F., Delamillieure, P., Millet, B., Olié, J. P., ... Vibert, N. (2011). A critical review of the contribution of eye movement recordings to the neuropsychology of obsessive compulsive disorder. *Acta Psychiatrica Scandinavica, 124*(2), 87–101. doi:10.1111/j.1600-0447.2011.01721.x

Karantinos, T., Tsoukas, E., Mantas, A., Kattoulas, E., Stefanis, N. C., Evdokimidis, I., & Smyrnis, N. (2014). Increased intra-subject reaction time variability in the volitional control of movement in schizophrenia. *Psychiatry Research, 215*(1), 26–32. doi:10.1016/j.psychres.2013.10.031

Kloft, L., Kischkel, E., Kathmann, N., & Reuter, B. (2011). Evidence for a deficit in volitional action generation in patients with obsessive-compulsive disorder. *Psychophysiology, 48*(6), 755–761. doi:10.1111/j.1469-8986.2010.01138.x

Kloft, L., Reuter, B., Riesel, A., & Kathmann, N. (2013). Impaired volitional saccade control: First evidence for a new candidate endophenotype in obsessive–compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience, 263*(3), 215–222. doi:10.1007/s00406-012-0331-x

Kloft, L., Reuter, B., Viswanathan, J., Kathmann, N., & Barton, J. J. (2012). Response selection in prosaccades, antisaccades, and other volitional saccades. *Experimental Brain Research, 222*(4), 345–353. doi:10.1007/s00221-012-3218-1

Lennertz, L., Rampacher, F., Vogeley, A., Schulze-Rauschenbach, S., Pukrop, R., Ruhrmann, S., ... Wagner, M. (2012). Antisaccade performance in patients with obsessive–compulsive disorder and unaffected relatives: Further evidence for impaired response inhibition as a candidate endophenotype. *European Archives of Psychiatry and Clinical Neuroscience, 262*(7), 625–634. doi:10.1007/s00406-012-0311-1

Leopold, R., & Backenstrass, M. (2015). Neuropsychological differences between obsessive-compulsive washers and checkers: A systematic review and meta-analysis. *Journal of Anxiety Disorders, 30*, 48–58. doi:10.1016/j.janxdis.2014.12.016

Maruff, P., Purcell, R., Tyler, P., Pantelis, C., & Currie, J. (1999). Abnormalities of internally generated saccades in obsessive–compulsive disorder. *Psychological Medicine, 29*(06), 1377–1385.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M. J., Speckens, A., & Phillips, M. L. (2004). Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Archives of General Psychiatry, 61*(6), 564–576. doi:10.1001/archpsyc.61.6.564

Mattheisen, M., Samuels, J. F., Wang, Y., Greenberg, B. D., Fyer, A. J., McCracken, J. T., ... Riddle, M. A. (2015). Genome-wide association study in obsessive-compulsive disorder: Results from the OCGAS. *Molecular Psychiatry, 20*(3), 337–344. doi:10.1038/mp.2014.43

McDowell, J. E., & Clementz, B. A. (1997). The effect of fixation condition manipulations on antisaccade performance in schizophrenia: Studies of

diagnostic specificity. *Experimental Brain Research, 115*(2), 333–344. doi:10.1007/PL00005702

McDowell, J. E., Dyckman, K. A., Austin, B. P., & Clementz, B. A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: Evidence from studies of humans. *Brain and Cognition, 68*(3), 255–270. doi:10.1016/j.bandc.2008.08.016

Menzies, L., Achard, S., Chamberlain, S. R., Fineberg, N., Chen, C. H., Del Campo, N., ... Bullmore, E. (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain, 130* (12), 3223–3236. doi:10.1093/brain/awm205

Montgomery, S. A., & Asberg, M. A. R. I. E. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*(4), 382–389. doi:10.1192/bjp.134.4.382

Munoz, D. P., Broughton, J. R., Goldring, J. E., & Armstrong, I. T. (1998). Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research, 121*(4), 391–400. doi:10.1007/s002210050473

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O. J., Liang, K. Y., LaBuda, M., ... Hoehn-Saric, R. (2000). A family study of obsessive-compulsive disorder. *Archives of General Psychiatry, 57*(4), 358–363. doi:10.1001/archpsyc.57.4.358

Neumann, N. U., & Schulte, R. M. (1989). *Montgomery and Asberg Depression Rating Scale. Deutsche Fassung*. Erlangen, Germany: Perimed Fachbuch Verlagsgesellschaft.

Nicolini, H., Arnold, P., Nestadt, G., Lanzagorta, N., & Kennedy, J. L. (2009). Overview of genetics and obsessive–compulsive disorder. *Psychiatry Research, 170*(1), 7–14. doi:10.1016/j.psychres.2008.10.011

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9*(1), 97–113. doi:10.1016/0028-3932(71)90067-4

Pauls, D. L., Alsobrook, J. P., Goodman, W., Rasmussen, S., & Leckmann, J. F. (1995). A family study of obsessive-compulsive disorder. *American Journal of Psychiatry, 152*(1), 76–84. doi:10.1176/ajp.152.1.76

Pirozzolo, F. J., & Rayner, K. (1980). Handedness, hemispheric specialization and saccadic eye movement latencies. *Neuropsychologia, 18*(2), 225–229. doi:10.1016/0028-3932(80)90068-8

Rajender, G., Bhatia, M. S., Kanwal, K., Malhotra, S., Singh, T. B., & Chaudhary, D. (2011). Study of neurocognitive endophenotypes in drug-naïve obsessive–

compulsive disorder patients, their first-degree relatives and healthy controls. *Acta Psychiatrica Scandinavica, 124*(2), 152–161. doi:10.1111/j.1600-0447.2011.01733.x

Reuter, B., Elsner, B., Möllers, D., & Kathmann, N. (2016). Decomposing mechanisms of abnormal saccade generation in schizophrenia patients: Contributions of volitional initiation, motor preparation, and fixation release. *Psychophysiology, 53*(11), 1712–1720. doi:10.1111/psyp.12729

Reuter, B., Jäger, M., Bottlender, R., & Kathmann, N. (2007). Impaired action control in schizophrenia: The role of volitional saccade initiation. *Neuropsychologia, 45*(8), 1840–1848. doi:10.1016/j.neuropsychologia.2006.12.006

Reuter, B., Kaufmann, C., Bender, J., Pinkpank, T., & Kathmann, N. (2010). Distinct neural correlates for volitional generation and inhibition of saccades. *Journal of Cognitive Neuroscience, 22*(4), 728–738. doi:10.1162/jocn.2009.21235

Reuter, B., Möllers, D., Bender, J., Schwehn, A., Ziemek, J., Gallinat, J., & Kathmann, N. (2011). Volitional saccades and attentional mechanisms in schizophrenia patients and healthy control subjects. *Psychophysiology, 48*(10), 1333–1339. doi:10.1111/j.1469-8986.2011.01213.x

Riesel, A., Endrass, T., Kaufmann, C., & Kathmann, N. (2011). Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: Evidence from unaffected first-degree relatives. *American Journal of Psychiatry, 168*(3), 317–324. doi:10.1176/appi.ajp.2010.10030416

Rosenberg, D. R., Dick, E. L., O'Hearn, K. M., & Sweeney, J. A. (1997). Response-inhibition deficits in obsessive-compulsive disorder: An indicator of dysfunction in frontostriatal circuits. *Journal of Psychiatry and Neuroscience, 22*(1), 29–38.

Sonuga-Barke, E. (2010). Disambiguating inhibitory dysfunction in attention-deficit/hyperactivity disorder: Toward the decomposition of developmental brain phenotypes. *Biological Psychiatry, 67*(7), 599–601. doi:10.1016/j.biopsych.2010.01.017

Spengler, D., Trillenberg, P., Sprenger, A., Nagel, M., Kordon, A., Junghanns, K., ... Lencer, R. (2006). Evidence from increased anticipation of predictive saccades for a dysfunction of frontostriatal circuits in obsessive–compulsive disorder. *Psychiatry Research, 143*(1), 77–88. doi:10.1016/j.psychres.2005.08.020

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1997). Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychological Reports, 80*(2), 443–446.

Stewart, S. E., Yu, D., Scharf, J. M., Neale, B. M., Fagerness, J. A., Mathews, C. A., ... McGrath, L. (2013). Genome-wide association study of obsessive-compulsive disorder. *Molecular Psychiatry, 18*(7), 788–798. doi:10.1038/mp.2012.85

Theleritis, C., Evdokimidis, I., & Smyrnis, N. (2014). Variability in the decision process leading to saccades: A specific marker for schizophrenia? *Psychophysiology, 51*(4), 327–336. doi:10.1111/psyp.12178

Pearlson, G. D., Machlin, S. R., Bylsma, F. W., & Hoehn-Saric, R. (1992). Oculomotor performance in obsessivecompulsive disorder. *American Journal of Psychiatry, 149*(5), 641–646. doi:10.1176/ajp.149.5.641

van den Heuvel, O. A., Remijnse, P. L., Mataix-Cols, D., Vrenken, H., Groenewegen, H. J., Uylings, H. B., ... Veltman, D. J. (2009). The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain, 132*(4), 853–868. doi:10.1093/brain/awn267

van der Wee, N. J., Hardeman, H. H., Ramsey, N. F., Raemaekers, M., Van Megen, H. J., Denys, D. A., ... Kahn, R. S. (2006). Saccadic abnormalities in psychotropic-naive obsessive-compulsive disorder without co-morbidity. *Psychological Medicine, 36*(9), 1321–1326. doi:1017/S0033291706007926

van Grootheest, D. S., Bartels, M., Van Beijsterveldt, C. E., Cath, D. C., Beekman, A. T., Hudziak, J. J., & Boomsma, D. I. (2008). Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. *Journal of the American Academy of Child & Adolescent Psychiatry, 47*(10), 1182–1188. doi:10.1097/CHI.0b013e3181825abd

Vergilino-Perez, D., Fayel, A., Lemoine, C., Senot, P., Vergne, J., & Doré-Mazars, K. (2012). Are there any left-right asymmetries in saccade parameters? Examination of latency, gain, and peak velocity. *Investigative Ophthalmology & Visual Science, 53*(7), 3340–3348. doi:10.1167/iovs.11-9273

Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Lee, C. K., ... Wittchen, H. U. (1994). The cross national epidemiology of obsessive-compulsive disorder. *Journal of Clinical Psychiatry, 55*(3 Suppl.), 5–10. doi:10.1017/S1092852900007136

Weissman, M. M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., & Olfson, M. (2000). Brief screening for family psychiatric history: The family history screen. *Archives of General Psychiatry, 57*(7), 675–682. doi:10.1001/pubs.ArchGenPsychiatry-ISSN-0003-990x-57-7-yoa8214

Wittchen, H. U., Zaudig, M., & Fydrich, T. (1997). *SKID. Strukturiertes klinisches Interview für DSM-IV. Achse I und II. Handanweisung [Structured Clinical Interview for DSM-IV. Axis I and II. Manual]*. Göttingen, Germany: Hogrefe.

Wöstmann, N. M., Aichert, D. S., Costa, A., Rubia, K., Möller, H. J., & Ettinger, U. (2013). Reliability and plasticity of response inhibition and interference control. *Brain and Cognition, 81*(1), 82–94. doi:10.1016/j.bandc.2012.09.010

Zhang, M., & Barash, S. (2000). Neuronal switching of sensorimotor transformations for antisaccades. *Nature, 408*(6815), 971–975. doi:10.1038/35050097

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ORIGINAL PAPER

Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder

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Abstract
Patients with obsessive-compulsive disorder (OCD) show dysfunctions of the fronto-striatal circuitry, which imply corresponding oculomotor deficits including smooth pursuit eye movements (SPEM). However, evidence for a deficit in SPEM is inconclusive, with some studies reporting reduced velocity gain while others did not find any SPEM dysfunctions in OCD patients. Interestingly, psychosis-like traits have repeatedly been linked to both OCD and impaired SPEM. Here, we examined a large sample of $n = 168$ patients with OCD, $n = 93$ unaffected first-degree relatives and $n = 171$ healthy control subjects to investigate whether elevated levels of schizotypy and SPEM deficits represent potential endophenotypes of OCD. We applied a SPEM task with high demands on predictive pursuit that is more sensitive to assess executive dysfunctions than a standard task with continuous visual feedback, as episodes of target blanking put increased demands on basal ganglia and prefrontal involvement. Additionally, we examined the relation between schizotypy and SPEM performance in OCD patients and their relatives. Results indicate that OCD patients and unaffected relatives do not show deficient performance in either standard or predictive SPEM. Yet, both patients and relatives exhibited elevated levels of schizotypy, and schizotypy was significantly correlated with velocity gain during standard trials in unmedicated and depression-free OCD patients. These findings highlight the role of schizotypy as a candidate endophenotype of OCD and add to the growing evidence for predisposing personality traits in OCD. Furthermore, intact gain may represent a key characteristic that distinguishes the OCD and schizophrenia patient populations.

Keywords Obsessive-compulsive disorder · OCD · Smooth pursuit eye movements · SPEM · Schizotypy · Endophenotype

1 Introduction

Obsessive-compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors), which affects 1–3% of the population worldwide [87]. Symptoms of OCD are highly heterogeneous across patients and cover dimensions of washing/contamination, ordering/symmetry, forbidden thoughts, and hoarding [6, 37]. Converging evidence from neuroimaging studies suggests that dysfunctions of the cortico-striato-thalamo-cortical circuits (CSTC) are implicated in the pathophysiology of OCD, resulting in disturbances of executive functioning [65], e.g., performance monitoring [70], planning [8], and working memory [30, 34]. Moreover, OCD patients exhibit deficits in a variety of oculomotor functions, including antisaccades [48], volitional saccades [40], and smooth pursuit eye movements [21].

Smooth pursuit eye movements (SPEM) enable us to track a small moving target with the eyes [43], like a car driving by in the distance or a pendulum swinging back and forth. In the investigation of SPEM, different waveforms can be used to separate the distinct underlying cognitive contributions of the SPEM system [2]. A widely used approach to study predictive mechanisms and velocity memory is to briefly blank the target during a ramp of ongoing SPEM [3]. Compared to a continuously visible target, blanking leads to the recruitment of the basal ganglia and additional prefrontal sources [44, 60]. Furthermore, predictive SPEM have been assumed to be associated with working memory [13, 58; however, see 39].

OCD has a strong genetic component with first-degree relatives having a fivefold increased risk on average to also be affected with the disease [26, 61, 66] and twin studies of OCD and OCD-related traits yielding heritability estimates around 50% [62, 82]. However, the identification of the specific genetic variants underlying this heritability proved to be difficult. Two genome-wide association studies (GWAS) and a recent meta-analysis of them did not find genome-wide significant hits [32, 55, 78]. Examining potential endophenotypes may aid in the identification of risk alleles as they are supposed to depend upon variation in fewer genes than the more complex disease phenotype and are, therefore, assumed to be more tractable to genetic analysis [25]. Within families, endophenotypes and the disorder co-segregate so that unaffected relatives are expected to show abnormalities similar to those observed in patients.

SPEM are a widely studied endophenotype of the psychosis spectrum, showing deficits in patients with psychotic disorders [45], their relatives [33, 38, 46], and healthy individuals displaying high levels of schizotypal traits [41]. As schizophrenia and OCD share a high genetic overlap [1, 11], endophenotypes of schizophrenia may be fruitful targets for OCD, as well. However, studies on SPEM in patients with OCD have yielded mixed results [35, 56] including findings of impaired continuous SPEM maintenance [21, 47, 79] and others of rather intact performance [12, 16, 77]. Most notably, the validity of these studies is limited by low statistical power due to small sample sizes. Until now, there is no research on predictive SPEM in OCD.

In accordance with the high comorbidity between schizophrenia and OCD [27, 67], patients with OCD have been found to display elevated schizotypal traits [71]. Thereby, schizotypy has been related to higher rates of symmetry/ordering obsessions, checking compulsions, aggressive obsessions, general psychopathology and overall obsessive symptom severity [7, 76, 85]. It has even been proposed that

OCD patients with high levels of schizotypy represent a subtype of OCD characterized by distinct deficits and genetic contributions [67]. For example, OCD patients with high levels of schizotypy show reductions in gray matter volume [42] as well as dorsolateral and frontal lobe dysfunction [29, 75] when compared to OCD patients with low levels of schizotypy. Notably, the overlap between OCD and schizophrenia appears to also be affected by neuroleptic medication, as clozapine treatment has been shown to induce OCD symptoms in schizophrenia patients [59, 72].

The aims of the present study were threefold. First, we aimed to investigate whether OCD patients and their unaffected first-degree relatives exhibit deficits in predictive SPEM. Given the CSTC dysfunctions in OCD and the increased demand on basal ganglia and prefrontal sources during episodes of target blanking, we hypothesized that a SPEM task that comprises episodes of blanking might be more sensitive to investigate executive dysfunctions in OCD than previously applied tasks with continuos visual feedback [35]. As distinct OCD symptom dimensions are associated with differences in brain structure [81], brain response to symptom provocation [54] and neuropsychological performance [49], we also investigated whether abnormalities in SPEM vary across OCD symptom dimensions. Second, we sought to examine whether elevated levels of schizotypy represent a potential endophenotype of OCD. Third, following the widely replicated findings of impaired SPEM in psychosis [63, 80] and high schizotypy [50, 83], we assessed the relationship between schizotypy and SPEM performance in OCD patients and unaffected first-degree relatives of patients with OCD.

2 Methods

2.1 Participants

168 patients with OCD, 171 healthy comparison subjects and 93 unaffected first-degree relatives of OCD patients participated in the study. Patients and controls were matched for age and gender ($p > 0.05$). Relatives showed a similar gender ratio, but were significantly older than patients and controls [$F(2,429) = 40.60$, $p < 0.001$; see Table 1 for sample characteristics]. OCD patients and relatives were recruited via the outpatient clinics at the Department of Psychology of Humboldt-Universität zu Berlin and at the Department of Psychiatry and Psychotherapy of the University of Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements. All participants were examined by trained clinical psychologists using

the Structured Clinical Interview for DSM-IV (SCID-I) [18, 86]. To establish cross-site reliability of clinical ratings, all instructions were standardized, and raters completed assessments of four training videos. Patients and relatives were only included if they were (1) free of past or present psychotic, bipolar, or substance related disorders, (2) did not take neuroleptic medication in the past 4 weeks and (3) did not use benzodiazepines in the past 2 weeks. Additionally, healthy controls were excluded if they (1) took any psychoactive medication in the past 3 months, (2) had a current axis-I disorder, (3) lifetime diagnosis of OCD or tic disorder, or (4) a family history of OCD. All relatives were free of past or present OCD. Moreover, all participants had normal or corrected-to-normal vision and were free of any neurological disease (lifetime).

Table 1. *Sample characteristics and SPEM performance of patients with OCD, unaffected first-degree relatives and healthy control subjects.*

	Patients with OCD	Unaffected first-degree relatives	Healthy control subjects	Statistic	*p*
N	168	93	171		
Mean age, years (*SD*)	33.32 (10.77)	46.65 (13.97)	34.09 (12.71)	$F(2,429) = 40.60$	< 0.001
Gender (% male)	42.9	31.2	39.2	$X^2(2) = 3.44$	0.18
Mean velocity gain during non-blanking trials (*SD*)	87.00 (12.01)	83.96 (12.65)	85.32 (13.65)	$F(2,429) = 1.80$	0.17
Mean velocity gain during blanking trials (*SD*)	41.16 (15.07)	37.92 (14.48)	40.53 (15.34)	$F(2,429) = 1.45$	0.24
Schizotypy (*SD*)	2.20 (1.74)	1.26 (1.57)	0.64 (0.94)	$F(2,426) = 50.82$	< 0.001
Mean OCI-R score (*SD*)	27.76 (12.03)	6.87 (6.57)	4.51 (4.49)	$F(2,427) = 351.74$	< 0.001
Mean Y-BOCS score (*SD*)	22.06 (6.81)	-	-		

Note. OCD, obsessive-compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; *SD*, Standard Deviation; SPEM, smooth pursuit eye movements; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

70 OCD patients were medicated with selective serotonin reuptake inhibitors (SSRIs) or other antidepressants. Furthermore, the majority of patients had one or more current comorbid axis-I disorder, with major depression being the most common comorbidity (n = 36 current episode, n = 66 remitted). The severity of obsessions and compulsions was assessed using the German version of the Yale–Brown Obsessive-

Compulsive Scale (Y–BOCS) [24, 28]. OCD symptom dimensions, i.e., washing, checking, ordering, obsessing, hoarding, and neutralizing, were measured via the Obsessive-Compulsive Inventory-Revised (OCI-R) [20, 23]. The self-report questionnaire of the Structured Clinical Interview for DSM-III-R Personality Disorders (SCIDII) [19] was used to assess schizotypal personality traits. Importantly, this measure of schizotypy does not include any items addressing pseudo-obsessive symptoms. Each of the questionnaire scales showed acceptable to high internal consistencies ($0.76 < \alpha < 0.93$).

Written informed consent was obtained and participants were compensated for their time with 10 € per hour. The study was in accordance with the revised Declaration of Helsinki, and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Clinic Bonn.

2.2 Eye movement recordings

Testing took place in a quiet, dimly lit room. Participants were seated comfortably in front of a 22-inch LCD monitor (Viewsonic; height 29.5 cm; width 47.5 cm; resolution 1680 × 1050 pixels; 60 Hz refresh rate) with a distance from eyes to screen of 70 cm. A chin rest was used to minimize head movements. At the Bonn assessment site, movements of the right eye were recorded using the EyeLink 1000 system (SR Research, Mississauga, Ontario, Canada) at a sampling frequency of 1000 Hz, whereas in Berlin, eye movements were recorded using the EyeLink II system (SR Research, Mississauga, Ontario, Canada) at a sampling rate of 250 Hz. Before the task started, the eye-tracker was calibrated with a five-point calibration task (0°, horizontal ± 13.3°, vertical ± 9.3°). Additionally, five practice trials were conducted immediately before the experimental sessions.

2.3 SPEM task and analysis

The SPEM task was implemented using ExperimentBuilder (SR Research, version 1.10.1241) and data analysis was performed with purpose-written routines in Matlab R2014a (The MathWorks, Natick, MA). Saccades were identified using the velocity (≥ 30°/s) and acceleration (≥ 8000°/s2) criteria of the SR research algorithm. Additionally, saccades were required to exhibit a minimum amplitude of ≥ 1°. SPEM were part of a larger oculomotor battery with additional tasks, of which the results were

already [4] and will be reported elsewhere. Completion of the whole battery took approximately 15 min.

In the SPEM task, the target moved horizontally in a triangular waveform (± 9.86° from the center) at a constant target velocity of 13°/s. During 44 of 89 half-cycles, the target was pseudo-randomly blanked off in the middle of the half-cycle for 500 ms. The duration of one half-cycle was 1500 ms. The main dependent variables were mean velocity gain scores at 900–1100 ms analogously in blanking and non-blanking half cycles. Thus, for blanking half-cycles, we received a mean residual gain score of 400–600 ms after target blanking [80]. Velocity gain was calculated using mean time-weighted and averaged scores for segments of pursuit with a minimum length of 50 ms (excluding blinks or saccades).

2.4 Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Release 23.0 (SPSS Inc., Chicago, IL, USA). First, main effects of blanking and age on velocity gain were investigated by analysis of covariance (ANCOVA) with blanking (blanking/non-blanking) as within-subject factor and age as covariate. To test the hypothesis of impaired SPEM in OCD patients and relatives, we conducted a 3 × 2 analysis of variance (ANOVA) with group as between-subject factor (OCD patients/unaffected first-degree relatives/healthy comparison subjects) and blanking (blanking/non-blanking) as within-subject factor. Group differences regarding schizotypal traits and OCD symptom dimensions as assessed by OCI-R were computed using one-way ANOVAs (OCD patients/unaffected first-degree relatives/healthy comparison subjects) and post hoc t tests. Furthermore, Pearson correlation coefficients were computed to explore relationships between oculomotor performance, OCD symptom dimensions and schizotypal traits in OCD patients and unaffected relatives. In these analyses, the significance threshold was set at $\alpha = 0.005$ to account for multiple comparisons while also considering inter-correlations between the different variables. All analyses were rerun excluding medicated patients and patients with depressive comorbidity ($n = 82$).

Dependent variables were screened for violation of normal distribution in both conditions and each of the three groups by Shapiro–Wilk tests [74], skewness scores and outliers. Homogeneity of variances was tested using Levene's test [22]. All post hoc tests were conducted using Bonferroni–Holm correction [31]. Effect sizes were

estimated using partial eta-squared [9] for ANOVAs and Cohen's *d* [10] for post hoc *t* tests.

3 Results

Across subjects, there was a strong effect of blanking [$F(1,430) = 736.60$, $p < 0.001$, $\eta^2 = 0.63$] indicating that velocity gain was smaller in blanking than in non-blanking trials. Age did not have a significant impact in terms of a main or an interaction effect [$F(1,430) = 0.17$, $p = 0.68$, $\eta^2 = 0.00$ and $F(1,430) = 0.11$, $p = 0.74$, $\eta^2 = 0.00$, respectively] and was hence not included in further analyses.

Analyzing SPEM in OCD patients, controls and unaffected relatives did not yield a significant effect of group or the group by blanking interaction [$F(2,429) = 1.86$, $p = 0.16$, $\eta^2 = 0.009$ and $F(2,429) = 0.45$, $p = 0.64$, $\eta^2 = 0.002$, respectively].

However, groups differed significantly regarding schizotypy [$F(2,426) = 50.82$, $p < 0.001$, $\eta^2 = 0.19$; Fig. 1] with patients exhibiting higher scores than relatives and controls (both $p < 0.001$; $d = 0.56$ and $d = 1.13$ respectively). Strikingly, unaffected relatives also showed elevated schizotypy compared to controls ($p = 0.002$, $d = 0.52$). OCD patients had significantly higher OCI-R scores than control subjects regarding the global scale and all symptom dimensions (all $p < 0.001$, $0.58 < d < 2.58$), while there were no significant differences between relatives and healthy controls in Bonferroni-corrected post hoc tests (all $p > 0.05$, $d < 0.41$).

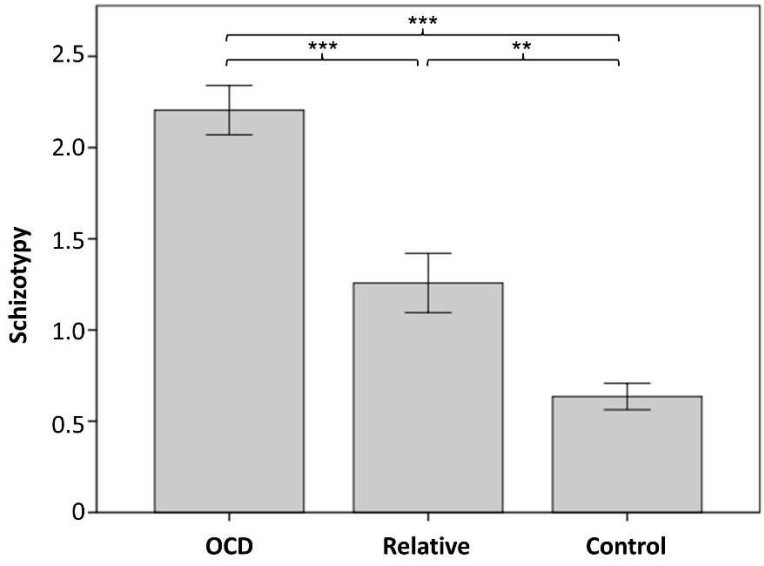

Fig. 1. Schizotypy as assessed by the SCID-II questionnaire in patients with obsessive-compulsive disorder (OCD), unaffected first-degree relatives and healthy controls. Error bars indicate standard errors. ** $p < .01$; *** $p < .001$.

In patients, schizotypy was nominally significantly associated with velocity gain during non-blanking ($r = -0.17$, $p = 0.034$), but not during blanking trials ($r = -0.07$, $p = 0.37$). Washing symptoms showed a negative correlation with gain during non-blanking trials ($r = -0.22$, $p = 0.005$), i.e., a higher severity of washing symptoms was related to poorer SPEM performance, whereas the other correlations between symptom dimensions and velocity gain did not remain significant after controlling for multiple comparisons ($p > 0.005$). Correlations between SPEM and symptom severity as assessed by Y–BOCS did not reach significance, either ($p > 0.005$).

Excluding medicated patients and patients with major depression did not change the results substantially. Notably, however, the correlations between velocity gain during non-blanking and schizotypal traits were more strongly pronounced when these patients were excluded ($r = -0.33$, $p = 0.003$).

4 Discussion

This is the first study to investigate predictive SPEM and schizotypy in OCD patients and their unaffected first-degree relatives. We did not observe any impairment in SPEM, but our findings provide novel evidence that schizotypy may represent a potential endophenotype of OCD, as both patients and unaffected relatives exhibited elevated scores compared to controls.

To the best of our knowledge, this is the largest study so far to assess SPEM in OCD, including up to nine times as many subjects as previous investigations, which have yielded inconsistent results. The missing association between OCD and velocity gain is hence very unlikely to be explained by a lack of statistical power. In accordance with the widely replicated SPEM deficits in schizophrenia patients [63] and the findings of Spengler et al. [77] and Damilou et al. [12], who observed impaired gain only in schizophrenia but not in OCD, our results support the assumption that intact gain may represent a key characteristic that distinguishes the two patient populations. Additionally, the correlations between schizotypal personality and SPEM gain in OCD patients (at least in the medication and major depression-free subsample) are in accordance with low SPEM performance in high schizotypes [41] and further support the close relationship between psychosis and SPEM performance. This finding also indicates that levels of schizotypy may represent a moderator contributing to mixed results across studies.

While schizotypy has only been discussed as an endophenotype of schizophrenia so far, the present results highlight its significance as a candidate endophenotype for OCD. The observation of elevated levels of schizotypy in OCD is in accordance with previously discussed overlaps between the diagnostic categories of OCD and schizophrenia, e.g., OCD symptoms in patients with schizophrenia [68, 84] and OCD symptoms induced or aggravated by second-generation antipsychotic drugs [17]. Schizotypal personality traits have a substantial genetic component, with twin studies yielding heritability estimates around 50% [15, 51]. Schizotypy is associated with OCD [71; present results] and elevated in unaffected relatives, which are key characteristics of an endophenotype. Moreover, schizotypy is easily and reliably measurable, making it a low-hanging fruit for future studies. As a potential endophenotype that is presumably less genetically complex and thus more tractable to genetic analysis [25], it may aid in the identification of genes predisposing an individual to develop OCD.

Our findings are in line with the growing evidence for shared genetic variation in OCD, schizophrenia, and common predisposing personality traits [1]. It has been shown that the presence of prior diagnosis of OCD is associated with an increased risk of developing schizophrenia later in life, and that offspring of parents diagnosed as having OCD have an increased risk of schizophrenia [57]. In addition to the strong genetic correlation between the two diseases, a substantial genetic overlap has been observed between schizotypy and neuroticism [52], which may partially mediate the genetic risk for both OCD and schizophrenia. Neuroticism has previously been discussed as an endophenotype of OCD, as levels of neuroticism and the related trait harm avoidance are increased in both OCD patients and relatives [5, 14, 73]. Considering the genetic overlap between neuroticism and schizotypy, it appears plausible that unaffected relatives of OCD patients also display elevated scores of schizotypy. The identification of multiple risk factors may eventually facilitate the identification of the genetic variants underlying OCD. Specifically, multivariate genetic approaches combining the analysis of disease phenotypes and endophenotypes may provide greater statistical power for detecting genetic variants than a univariate approach based on either phenotype alone [64].

A relevant factor that might play an important role in the explanation of inconsistent findings across studies is variability in OCD symptom dimensions. We found that washing symptoms were negatively associated with gain during non-

blanking trials. Though SPEM performance has not been investigated in relation to OCD symptom dimensions so far, a variety of studies has assessed the impact of symptom dimensions on neuropsychological performance measures associated with SPEM, e.g., working memory [13, 58]. While for the majority of cognitive functions, patients with checking compulsions showed larger impairments than patients with washing symptoms in a recent meta-analysis, no significant differences between these groups were found with regard to working memory [49]. In a large study that used a dimensional rather than a categorical approach, washing symptoms were associated with worse working memory performance [36], which is in line with our findings of impaired SPEM. However, further research is clearly warranted to investigate the association between washing symptoms and predictive SPEM in more detail.

The present study is not without limitations. Notably, relatives were significantly older than OCD patients and controls. However, there were no main or interaction effects of age on SPEM performance, making this issue unlikely to account for the absent group difference. While we observed a significant association between schizotypy and SPEM dysfunction in OCD patients, this correlation did not reach significance in relatives, presumably due to low variance in schizotypy. Though the SCID-II questionnaire for personality disorders is a valid measure, other inventories that comprise more items like the Schizotypal Personality Questionnaire (SPQ) [69] or the Oxford–Liverpool Inventory of Feelings and Experiences [53] may have been more sensitive to differences between relatives and controls, and would have allowed for subscale analyses of positive and negative symptoms of schizotypy. Future studies may thus want to employ more elaborate questionnaires. Strengths of our study are the large sample size, the detailed characterization of subjects and the consideration of medication and comorbidity effects.

In conclusion, OCD patients and unaffected relatives did not show deficient performance in either sustained or predictive SPEM. However, both patients and relatives exhibited elevated levels of schizotypy, providing first evidence for a candidate endophenotype of OCD.

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Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

References

1. Anttila V, Bulik-Sullivan B, Finucane HK, Bras J, Duncan L, Escott-Price V et al (2016) Analysis of shared heritability in common disorders of the brain. BioRxiv. https://doi.org/10.1101/048991
2. Barnes GR (2008) Cognitive processes involved in smooth pursuit eye movements. Brain Cogn 68(3):309–326. https://doi.org/10.1016/j.bandc.2008.08.020
3. Becker W, Fuchs AF (1985) Prediction in the oculomotor system: smooth pursuit during transient disappearance of a visual target. Exp Brain Res 57(3):562–575. https://doi.org/10.1007/BF00237843
4. Bey K, Kloft L, Lennertz L, Grützmann R, Heinzel S, Kaufmann C, Wagner M (2017) Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives. Psychophysiology 54(9):1284–1294. https://doi.org/10.1111/psyp.12884
5. Bey K, Lennertz L, Riesel A, Klawohn J, Kaufmann C, Heinzel S, Wagner M (2017) Harm avoidance and childhood adversities in patients with obsessive-compulsive disorder and their unaffected first-degree relatives. Acta Psychiatr Scand 135(4):328–338. https://doi.org/10.1111/acps.12707
6. Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF (2008) Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am J Psychiatry 165(12):1532–1542. https://doi.org/10.1176/appi.ajp.2008.08020320
7. Brakoulias V, Starcevic V, Berle D, Milicevic D, Hannan A, Viswasam K, Mann K (2014) The clinical characteristics of obsessive compulsive disorder associated with high levels of schizotypy. Aust N Z J Psychiatry 48(9):852–860. https://doi.org/10.1177/00048 67414531831
8. Cavedini P, Zorzi C, Piccinni M, Cavallini MC, Bellodi L (2010) Executive dysfunctions in obsessive-compulsive patients and unaffected relatives: searching for a new intermediate phenotype. Biol Psychiat 67(12):1178–1184. https://doi.org/10.1016/j.biopsych.2010.02.012

9. Cohen J (1973) Eta-squared and partial eta-squared in fixed factor anova designs. Educ Psychol Measur 33(1):107–112. https://doi.org/10.1177/001316447303300111
10. Cohen J (1988) Statistical power analysis for the behavioral sciences (2nd ed). Academic Press, New York
11. Costas J, Carrera N, Alonso P, Gurriarán X, Segalàs C, Real E, Morell M (2016) Exon-focused genome-wide association study of obsessive-compulsive disorder and shared polygenic risk with schizophrenia. Transl Psychiatry 6(3):e768. https://doi.org/10.1038/tp.2016.34
12. Damilou A, Apostolakis S, Thrapsanioti E, Theleritis C, Smyrnis N (2016) Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. Psychophysiology 53(6):796–805. https://doi.org/10.1111/psyp.12630
13. Ding J, Powell D, Jiang Y (2009) Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. Hum Brain Mapp 30(11):3541–3552. https://doi.org/10.1002/hbm.20777
14. Ettelt S, Grabe HJ, Ruhrmann S, Buhtz F, Hochrein A, Kraft S, John U (2008) Harm avoidance in subjects with obsessive-compulsive disorder and their families. J Affect Disord 107(1):265–269. https://doi.org/10.1016/j.jad.2007.08.017
15. Ericson M, Tuvblad C, Raine A, Young-Wolff K, Baker LA (2011) Heritability and longitudinal stability of schizotypal traits during adolescence. Behav Genet 41(4):499–511. https://doi.org/10.1007/s10519-010-9401-x
16. Farber RH, Clementz BA, Swerdlow NR (1997) Characteristics of open- and closed loop smooth pursuit responses among obsessive-compulsive disorder, schizophrenia, and nonpsychiatric individuals. Psychophysiology 34:157–162
17. Fernandez-Egea E, Worbe Y, Bernardo M, Robbins TW (2018) Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia. Psychol Med. https://doi.org/10.1017/S003329171800017X
18. First MB, Spitzer RL, Gibbon M, Williams JB (1997) User's guide for the Structured Clinical Interview for DSM-IV axis I Disorders SCID-I: clinician version. American Psychiatric Association Publishing, Arlington
19. First MB, Spitzer RL, Gibbon M, Williams JB, Davies M, Borus J, Rounsaville B (1995) The structured clinical interview for DSM-III-R personality disorders

(SCID-II). Part II: multi-site test-retest reliability study. J Pers Disord 9(2):92–104. https://doi.org/10.1521/pedi.1995.9.2.92

20. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, Salkovskis PM (2002) The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess 14(4):485–496. https://doi.org/10.1037/1040-3590.14.4.485
21. Gambini O, Abbruzzese M, Scarone S (1993) Smooth pursuit and saccadic eye movements and Wisconsin card sorting test performance in obsessive-compulsive disorder. Psychiatry Res 48(3):191–200. http://www.ncbi.nlm.nih.gov/pubmed/82724 42
22. Glass GV (1966) Testing homogeneity of variances. Am Educ Res J 3(3):187–190
23. Gönner S, Leonhart R, Ecker W (2008) The obsessive-compulsive inventory-revised (OCI-R): validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. J Anxiety Disord 22(4):734–749. https://doi.org/10.1016/j.janxd is.2007.07.007
24. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS (1989) The Yale Brown obsessive compulsive scale: II. Validity. Arch Gen Psychiatry 46(11):1012–1016. https://doi.org/10.1001/archpsyc.1989.01810110054008
25. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160(4):636–645. https://doi.org/10.1176/appi.ajp.160.4.636
26. Grabe HJ, Ruhrmann S, Ettelt S, Buhtz F, Hochrein A, Schulze-Rauschenbach S, Freyberger HJ (2006) Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. Am J Psychiatry 163(11):1986–1992. https://doi.org/10.1176/ajp.2006.163.11.1986
27. Grover S, Dua D, Chakrabarti S, Avasthi A (2017) Obsessive compulsive symptoms/disorder in patients with schizophrenia: prevalence, relationship with other symptom dimensions and impact on functioning. Psychiatry Res 250:277–284. https://doi.org/10.1016/j.psychres.2017.01.067
28. Hand I, Büttner-Westphal H (1991) Die Yale-Brown obsessive compulsive scale (Y-BOCS): Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen [The Yale-Brown Obsessive Compulsive

Scale: a semistructured interview to assess the severity of obsessions and compulsions]. Verhaltenstherapie 1(3):223–225

29. Harris CL, Dinn WM (2003) Subtyping obsessive-compulsive disorder: neuropsychological correlates. Behav Neurol 14(3–4):75–87. https://doi.org/10.1155/2003/782718
30. Heinzel S, Kaufmann C, Grützmann R, Hummel R, Klawohn J, Riesel A, Kathmann N (2018) Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder. Neuroimage Clin 17:426–434. https://doi.org/10.1016/j.nicl.2017.10.039
31. Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 6(2):65–70
32. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2017). Revealing the complex genetic architecture of obsessive-compulsive disorder using metaanalysis. Mol Psychiatry. https://doi.org/10.1038/mp.2017.154
33. Ivleva EI, Moates AF, Hamm JP, Bernstein IH, O'Neill HB, Cole D, Tamminga CA (2014) Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. Schizophr Bull 40(3):642–652. https://doi.org/10.1093/schbul/sbt047
34. Jaafari N, Frasca M, Rigalleau F, Rachid F, Gil R, Olié JP, Vibert N (2013) Forgetting what you have checked: a link between working memory impairment and checking behaviors in obsessivecompulsive disorder. Eur Psychiatry 28(2):87–93. https://doi.org/10.1016/j.eurpsy.2011.07.001
35. Jaafari N, Rigalleau F, Rachid F, Delamillieure P, Millet B, Olié J-PP, Vibert N (2011) A critical review of the contribution of eye movement recordings to the neuropsychology of obsessive compulsive disorder. Acta Psychiatr Scand 124(2):87–101. https://doi.org/10.1111/j.1600-0447.2011.01721.x
36. Kashyap H, Kumar JK, Kandavel T, Reddy YCJ (2017) Relationships between neuropsychological variables and factor-analysed symptom dimensions in obsessive compulsive disorder. Psychiatry Res 249:58–64. https://doi.org/10.1016/j.psychres.2016.12.044

37. Kathmann N (2015) Obsessive-Compulsive Disorder across the Life Span. In: James D, Wright (eds) International encyclopedia of the social & behavioral sciences, vol 17, 2nd edn. Elsevier, Oxford, pp 119–126. https://doi.org/10.1016/B978-0-08-097086-8.21021-0 (**ISBN: 9780080970868**)
38. Kathmann N, Hochrein A, Uwer R, Bondy B (2003) Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. Am J Psychiatry 160:696–702
39. Kattoulas E, Smyrnis N, Stefanis NC, Avramopoulos D, Stefanis CN, Evdokimidis I (2011) Predictive smooth eye pursuit in a population of young men: I. Effects of age, IQ, oculomotor and cognitive tasks. Exp Brain Res 215(3–4):207–218. https://doi.org/10.1007/s00221-011-2887-5
40. Kloft L, Kischkel E, Kathmann N, Reuter B (2011) Evidence for a deficit in volitional action generation in patients with obsessivecompulsive disorder. Psychophysiology 48(6):755–761. https://doi.org/10.1111/j.1469-8986.2010.01138.x
41. Koychev I, Joyce D, Barkus E, Ettinger U, Schmechtig A, Dourish CT, Deakin JFW (2016) Cognitive and oculomotor performance in subjects with low and high schizotypy: implications for translational drug development studies. Transl Psychiatry 6(5):1–8. https://doi.org/10.1038/tp.2016.64
42. Lee KJ, Shin YW, Wee H, Kim YY, Kwon JS (2006) Gray matter volume reduction in obsessive-compulsive disorder with schizotypal personality trait. Prog Neuropsychopharmacol Biol Psychiatry 30(6):1146–1149. https://doi.org/10.1016/j.pnpbp.2006.03.022
43. Leigh JR, Zee DS (2015) The neurology of eye movements. Oxford University Press, Oxford. https://doi.org/10.1093/med/9780199969289.001.0001
44. Lencer R, Nagel M, Sprenger A, Zapf S, Erdmann C, Heide W, Binkofski F (2004) Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. Eur J Neurosci 19(5):1430–1436. https://doi.org/10.1111/j.1460-9568.2004.03229.x
45. Lencer R, Reilly JL, Harris MS, Sprenger A, Keshavan MS, Sweeney JA (2010) Sensorimotor transformation deficits for smooth pursuit in first-episode affective psychoses and schizophrenia. Biol Psychiat 67(3):217–223. https://doi.org/10.1016/j.biopsych.2009.08.005

46. Lencer R, Sprenger A, Reilly JL, McDowell JE, Rubin LH, Badner JA, Sweeney JA (2015) Pursuit eye movements as an intermediate phenotype across psychotic disorders: evidence from the B-SNIP study. Schizophr Res 169(1–3):326–333. https://doi.org/10.1016/j.schres.2015.09.032
47. Lencer R, Trillenberg P, Trillenberg-Krecker K, Junghanns K, Kordon A, Brooks A, Arolt V (2004) Smooth pursuit deficits in schizophrenia, affective disorder and obsessive-compulsive disorder. Psychol Med 34(3):451–460. https://doi.org/10.1017/S0033291703001314
48. Lennertz L, Rampacher F, Vogeley A, Schulze-Rauschenbach S, Pukrop R, Ruhrmann S, Wagner M (2012) Antisaccade performance in patients with obsessive-compulsive disorder and unaffected relatives: further evidence for impaired response inhibition as a candidate endophenotype. Eur Arch Psychiatry Clin Neurosci 262(7):625–634. https://doi.org/10.1007/s00406-012-0311-1
49. Leopold R, Backenstrass M (2015) Neuropsychological differences between obsessive-compulsive washers and checkers: a systematic review and meta-analysis. J Anxiety Disord 30:48–58. https://doi.org/10.1016/j.janxdis.2014.12.016
50. Lenzenweger MF, O'driscoll GA (2006) Smooth pursuit eye movement and schizotypy in the community. J Abnorm Psychol 115(4):779. https://doi.org/10.1037/0021-843X.115.4.779
51. Linney YM, Murray RM, Peters ER, MacDonald AM, Rijsdijk F, Sham PC (2003) A quantitative genetic analysis of schizotypal personality traits. Psychol Med 33(5):803–816. https://doi.org/10.1017/S0033291703007906
52. Macare C, Bates TC, Heath AC, Martin NG, Ettinger U (2012) Substantial genetic overlap between schizotypy and neuroticism: a twin study. Behav Genet 42(5):732–742. https://doi.org/10.1007/s10519-012-9558-6
53. Mason O, Linney Y, Claridge G (2005) Short scales for measuring schizotypy. Schizophr Res 78(2–3):293–296. https://doi.org/10.1016/j.schres.2005.06.020
54. Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML (2004) Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry 61(6):564–576. https://doi.org/10.1001/archpsyc.61.6.564

55. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, Riddle MA (2015) Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry 20(3):337–344. https://doi.org/10.1038/mp.2014.43
56. McCarthy MJ (2011) The eyes are the window to the brain: reviewing oculomotor abnormalities in obsessive-compulsive disorder. Acta Psychiatr Scand 124(2):85–86. https://doi.org/10.1111/j.1600-0447.2011.01732.x
57. Meier SM, Petersen L, Pedersen MG, Arendt MC, Nielsen PR, Mattheisen M, Mortensen PB (2014) Obsessive-compulsive disorder as a risk factor for schizophrenia: a nationwide study. JAMA Psychiatry 71(11):1215–1221. https://doi.org/10.1001/jamapsychiatry.2014.1011
58. Moates AF, Ivleva EI, O'Neill HB, Krishna N, Cullum CM, Thaker GK, Tamminga CA (2012) Predictive pursuit association with deficits in working memory in psychosis. Biol Psychiat 72(9):752–757. https://doi.org/10.1016/j.biopsych.2012.03.030
59. Mukhopadhaya K, Krishnaiah R, Taye T, Nigam A, Bailey AJ, Sivakumaran T, Fineberg NA (2009) Obsessive-compulsive disorder in UK clozapine-treated schizophrenia and schizoaffective disorder: a cause for clinical concern. J Psychopharmacol 23(1):6–13. https://doi.org/10.1177/0269881108089582
60. Nagel M, Sprenger A, Hohagen F, Binkofski F, Lencer R (2008) Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. NeuroImage 41(2):483–492. https://doi.org/10.1016/j.neuroimage.2008.02.058
61. Nestadt G, Samuels J, Riddle M, Bienvenu OJ, Liang KY, LaBuda M, Hoehn-Saric R (2000) A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 57(4):358–363. https://doi.org/10.1001/archpsyc.57.4.358
62. Nicolini H, Arnold P, Nestadt G, Lanzagorta N, Kennedy JL (2009) Overview of genetics and obsessive-compulsive disorder. Psychiatry Res 170(1):7–14. https://doi.org/10.1016/j.psychres.2008.10.011
63. O'Driscoll GA, Callahan BL (2008) Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993. Brain Cogn 68(3):359–370. https://doi.org/10.1016/j.bandc.2008.08.023

64. O'Reilly PF, Hoggart CJ, Pomyen Y, Calboli FC, Elliott P, Jarvelin MR, Coin LJ (2012) MultiPhen: joint model of multiple phenotypes can increase discovery in GWAS. PloS One 7(5):e34861. https://doi.org/10.1371/journal.pone.0034861
65. Pauls DL, Abramovitch A, Rauch SL, Geller DA (2014) Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci 15(6):410–424. https://doi.org/10.1038/nrn3746
66. Pauls DL, Alsobrook JP II, Goodman W, Rasmussen S, Leckman JF (1995) A family study of obsessive-compulsive disorder. Am J Psychiatry 152(1):76–84. https://doi.org/10.1176/ajp.152.1.76
67. Poyurovsky M, Koran LM (2005) Obsessive-compulsive disorder (OCD) with schizotypy vs. schizophrenia with OCD: diagnostic dilemmas and therapeutic implications. J Psychiatr Res 39(4):399–408. https://doi.org/10.1016/j.jpsychires.2004.09.004
68. Poyurovsky M, Zohar J, Glick I, Koran LM, Weizman R, Tandon R, Weizman A (2012) Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. Compr Psychiatry 53(5):480–483
69. Raine A (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull 17(4):555. https://doi.org/10.1093/schbul/17.4.555
70. Riesel A, Endrass T, Kaufmann C, Kathmann N (2011) Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: evidence from unaffected firstdegree relatives. Am J Psychiatry 168(3):317–324. https://doi.org/10.1176/appi.ajp.2010.10030416
71. Rossi A, Daneluzzo E (2002) Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. Schizophr Res 54(1–2):67–75. https://doi.org/10.1016/S0920-9964(01)00353-X
72. Sa AR, Hounie AG, Sampaio AS, Arrais J, Miguel EC, Elkis H (2009) Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol. Compr Psychiatry 50(5):437–442. https://doi.org/10.1016/j.comppsych.2008.11.005
73. Samuels J, Nestadt G, Bienvenu OJ, Costa PT, Riddle MA, Liang KY, Cullen BA (2000) Personality disorders and normal personality dimensions in obsessive—compulsive disorder. Br J Psychiatry 177(5):457–462. https://doi.org/10.1192/bjp.177.5.457

74. Shapiro SS, Wilk MB (1965) An analysis of variance test for normality (complete samples). Biometrika 52(3/4):591. https://doi.org/10.2307/2333709
75. Shin NY, Lee AR, Park HY, Yoo SY, Kang DH, Shin MS, Kwon JS (2008) Impact of coexistent schizotypal personality traits on frontal lobe function in obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 32(2):472–478. https://doi.org/10.1016/j.pnpbp.2007.09.020
76. Sobin C, Blundell ML, Weiller F, Gavigan C, Haiman C, Karayiorgou M (2000) Evidence of a schizotypy subtype in OCD. J Psychiatric Res 34(1):15–24. http://www.ncbi.nlm.nih.gov/pubmed/10696829
77. Spengler D, Trillenberg P, Sprenger A, Nagel M, Kordon A, Junghanns K, Lencer R (2006) Evidence from increased anticipation of predictive saccades for a dysfunction of fronto-striatal circuits in obsessive-compulsive disorder. Psychiatry Res 143(1):77–88. https://doi.org/10.1016/j.psychres.2005.08.020
78. Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, McGrath L (2013) Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry 18(7):788–798. https://doi.org/10.1038/mp.2012.85
79. Sweeney JA, Palumbo DR, Shear MK, Halper JP (1992) Pursuit eye movement dysfunction in obsessive-compulsive disorder. Psychiatry Res 42:1–11
80. Trillenberg P, Sprenger A, Talamo S, Herold K, Helmchen C, Verleger R, Lencer R (2017) Visual and non-visual motion information processing during pursuit eye tracking in schizophrenia and bipolar disorder. Eur Arch Psychiatry Clin Neurosci 267(3):225–235. https://doi.org/10.1007/s00406-016-0671-z
81. van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, Veltman DJ (2009) The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain 132(4):853–868. https://doi.org/10.1093/brain/awn26 7
82. Van Grootheest DS, Bartels M, Van Beijsterveldt CE, Cath DC, Beekman AT, Hudziak JJ, Boomsma DI (2008) Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. J Am Acad Child Adolesc Psychiatry 47(10):1182–1188. https://doi.org/10.1097/CHI.0b013e3181825abd
83. van Kampen D, Deijen JB (2009) SPEM dysfunction and general schizotypy as measured by the SSQ: a controlled study. BMC Neurol 9(1):27. https://doi.org/10.1186/1471-2377-9-27

84. Vrbova K, Prasko J, Cinculova A, Krnacova B, Talova B, Tichackova A, Latalova K (2017) Schizophrenia and obsessive compulsive disorder. Eur Psychiatry 41:S844
85. Yamamoto H, Tsuchida H, Nakamae T, Nishida S, Sakai Y, Fujimori A, Fukui K (2012) Relationship between severity of obsessive-compulsive symptoms and schizotypy in obsessivecompulsive disorder. Neuropsychiatr Dis Treat 8:579–583. https://doi.org/10.2147/NDT.S38450
86. Wittchen HU, Zaudig M, Fydrich T (1997) Skid. Strukturiertes klinisches Interview für DSM-IV. Achse I und II. Handanweisung [Structured Clinical Interview for DSM-IV. Axis I and II. Hogrefe, Manual]. Göttingen
87. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, Wittchen HU (1994) The cross national epidemiology of obsessive-compulsive disorder. J Clin Psychiatry 55(3 Suppl.):5–10. https://doi.org/10.1017/S1092852900007136

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Impaired planning in patients with obsessive-compulsive disorder and unaffected first-degree relatives: Evidence for a cognitive endophenotype

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ABSTRACT

Patients with obsessive-compulsive disorder (OCD) show deficient planning capacity in the Tower of London (TOL) problem solving task. Preliminary evidence for similar deficits in unaffected first-degree relatives suggests that impaired planning may constitute an endophenotype of OCD. However, results on this issue are inconsistent, possibly owing to small sample sizes and variability in problem structure across TOL tasks. Here, we adopted a computerized version of the TOL task featuring a 2×2 factorial design (high/low search depth × full/partial tower goal state) and examined a well-characterized sample of $n = 72$ OCD patients, $n = 76$ unaffected first-degree relatives and $n = 102$ healthy comparison subjects. Both OCD patients and relatives exhibited significantly less accurate problem solving than controls. Search depth, goal hierarchy, or the number of minimum moves did not moderate these group differences. Medication, OCD symptoms, and depressive comorbidity did not affect TOL performance in patients, suggesting a state-independent effect. In conclusion, we found that OCD patients as well as unaffected first-degree relatives show deficient TOL performance across a range of task conditions, strongly supporting the role of impaired planning as an endophenotype of OCD, and contributing to the growing evidence for fronto-striatal dysfunctions in OCD.

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Impaired Antisaccades in Obsessive-Compulsive Disorder: Evidence From Meta-Analysis and a Large Empirical Study

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Increasing evidence indicates that patients with obsessive-compulsive disorder (OCD) exhibit alterations in fronto-striatal circuitry. Performance deficits in the antisaccade task would support this model, but results from previous small-scale studies have been inconclusive as either increased error rates, prolonged antisaccade latencies, both or neither have been reported in OCD patients. In order to address this issue, we investigated antisaccade performance in a large sample of OCD patients (n = 169) and matched control subjects (n = 183). As impaired antisaccade performance constitutes a potential endophenotype of OCD, unaffected first-degree relatives of OCD patients (n = 100) were assessed, as well. Furthermore, we conducted a quantitative meta-analysis to integrate our data with previous findings. In the empirical study, OCD patients exhibited significantly increased antisaccade latencies, intra-subject variability (ISV) of antisaccade latencies, and antisaccade error rates. The latter effect was driven by errors with express latency (80–130 ms), as patients did not differ significantly from controls with regards to regular errors (>130 ms). Notably, unaffected relatives of OCD patients showed elevated antisaccade express error rates and increased ISV of antisaccade latencies, as well. Antisaccade performance was not associated with state anxiety within groups. Among relatives, however, we observed a significant correlation between antisaccade error rate and harm avoidance. Medication status of OCD patients, symptom severity, depressive comorbidity, comorbid anxiety disorders and OCD symptom dimensions did not significantly affect antisaccade performance. Meta-analysis of 10 previous and the present empirical study yielded a medium-sized effect (SMD = 0.48, $p < 0.001$) for higher error rates in OCD patients, while the effect for latencies did not reach significance owing to strong heterogeneity (SMD = 0.51, p = 0.069). Our results support the assumption of impaired antisaccade performance in OCD, although effects sizes were only moderately large. Furthermore, we provide the

first evidence that increased antisaccade express error rates and ISV of antisaccade latencies may constitute endophenotypes of OCD. Findings regarding these more detailed antisaccade parameters point to potentially underlying mechanisms, such as early pre-stimulus inhibition of the superior colliculus.

Keywords: obsessive-compulsive disorder, OCD, antisaccade, endophenotype, meta-analysis, eye-tracking

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (recurrent intrusive thoughts and/or images) and/or compulsions (ritualized repetitive behaviors), that affects 1–3% of the population worldwide (1). OCD is familial (2) with first-degree relatives having an approximately 5-fold increased risk of also being affected by the disease (3–5). Converging evidence from neuroimaging studies has suggested that altered functioning of the cortico-striato-thalamo-cortical (CSTC) circuits, including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), basal ganglia and the thalamus, is implicated in the pathophysiology of OCD (6, 7). Specifically, an imbalance between the direct and indirect pathways within the CSTC circuits leads to an excess tone in the former over the latter, resulting in disturbances of executive functioning that may underlie features of the symptomatology of OCD (8). While the direct loop functions as a self-reinforcing positive feedback loop and contributes to the initiation and continuation of behaviors, the indirect loop serves as a mechanism of negative feedback, which is implicated in the inhibition of behaviors and in adaptive switching between behaviors (9, 10). The CSTC model of OCD thus predicts that affected individuals will be characterized by impaired performance in executive function tasks that demand the initiation of a volitional response while inhibiting a prepotent response.

A well-established approach to investigating those functions is the antisaccade task (11), which requires subjects to suppress a reflexive saccade toward a peripherally appearing stimulus in order to make a volitional eye movement in the opposite direction. As a control condition featuring the same setup but with no inhibitory demands, the prosaccade task has been used, which instructs the subject to look toward the appearing stimulus. While OCD patients perform normally with respect to prosaccade tasks in terms of error rates, latencies [for a review, see (12)] and intra-subject variability (ISV) of latencies (13), research employing the antisaccade task provides more mixed results, with a range of studies describing deficits in either error rates, latencies, both or neither (14–23). Inconsistencies in results may be explained by a variety of factors, including differences in task design parameters and sample characteristics. Across patients, obsessive-compulsive symptoms are highly heterogeneous, covering dimensions of washing/contamination, ordering/symmetry, forbidden thoughts and hoarding (24), which are all associated with differences in brain structure (25), brain function (26, 27) and neuropsychological performance (28). The interpretation of findings pertaining to the antisaccade task is further hindered by the tendency to utilize small sample sizes so that in certain cases, non-significant group differences might reflect poor statistical power rather than an absence of effect. Still, a quantitative meta-analysis of antisaccade performance in OCD is lacking, and the examination of larger samples of well-characterized OCD patients is warranted. The investigation of antisaccade performance in OCD could also benefit from examining more fine-grained outcome measures, like, for example, by subdividing direction errors into express errors and regular errors as distinct mechanisms appear to act as the foundation of these different types of errors (29). Errors with express latency ($\leq$130 ms) result from failed preparatory suppression of the superior colliculus that must be present prior to stimulus appearance in order to prevent a reflexive orienting response toward the peripheral stimulus. Errors with regular latency (>130 ms), on the other hand, result from failure in active suppression of an automated saccade plan and the generation of a voluntary saccade to an abstract location. As these detailed saccade parameters have not been investigated in OCD patients so far, the analysis of express and regular error rates may point to specific neural mechanism deficient in OCD. Furthermore, functional and structural aberrations in OCD are not restricted to "executive" loops within the CSTC circuitry but also concern interconnected "affective" circuits that underlie functions of reward sensitivity, fear extinction and anxiety proneness (30, 31). Considering anxiety-related traits like harm avoidance in the context of antisaccade research may hence yield additional insights.

As response inhibition has been proposed as a potential endophenotype of OCD, the assessment of unaffected first-degree relatives might also prove fruitful in the search for the biological underpinnings of OCD. Endophenotypes are quantitative variables (e.g., cognitive or neurophysiological) associated with the disease while being distinct from the clinical phenotype itself (32). They are supposed to depend upon variation in fewer genes than the more complex disease phenotype and are therefore assumed to be more tractable to genetic analysis. Within families, endophenotypes and the disorder co-segregate, so that unaffected relatives are expected to show abnormalities similar to those observed in patients. In line with this concept, both OCD patients and relatives exhibit deficits in performance monitoring (33), planning capacity (34), cognitive flexibility (34–36) and response inhibition as evaluated with the Stop Signal Task (35, 37) and the Stroop Task (36). Most notably, Lennertz et al. (17) recently reported deficient antisaccade performance in OCD patients as well as in their unaffected first-degree relatives in terms of both elevated error rates and increased antisaccade latencies.

In the present study, we aimed to investigate whether patients with OCD and their first-degree relatives exhibit deficits in the antisaccade task by assessing error rates, mean latencies and ISV of latencies in a large and well-characterized sample. In addition, we conducted a quantitative meta-analysis to integrate our data with previous findings and quantify random and systematic influences on the results.

MATERIALS AND METHODS

Empirical Study

Participants

One hundred and sixty-nine patients with OCD, 183 healthy comparison subjects and 100 unaffected first-degree relatives of OCD patients ($n = 67$ parents; $n = 25$ siblings; $n = 8$ offspring) participated in the study. Patients and controls were matched for age, gender and education. Relatives were significantly older than patients and controls (see **Table 1** for sample characteristics). OCD patients and relatives were recruited via the outpatient clinics at the Department of Psychology of Humboldt-Universität zu Berlin and at the Department of Psychiatry and Psychotherapy of the University of Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements. A total of 279 subjects were assessed in Berlin ($n = 101$ OCD patients; $n = 54$ unaffected relatives; $n = 124$ control subjects) and 171 subjects were assessed in Bonn ($n = 68$ OCD patients; $n = 46$ unaffected relatives; $n = 59$ control subjects). All participants were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV [SCID-I; (38, 39)]. To establish cross-site reliability of clinical ratings, all instructions were standardized and raters completed assessments of four training videos. Patients and relatives were only included if they were: (a) free of past or present psychotic, bipolar or substance-related disorders; (b) did not take neuroleptic medication for the previous 4 weeks; and (c) did not use benzodiazepines in the prior 2 weeks. Additionally, healthy controls were excluded if they: (a) took any psychoactive medication in the previous 3 months; (b) had a current Axis I disorder; (c) had a lifetime diagnosis of OCD or tic disorder; or (d) had a family history of OCD. All relatives were free of past or present OCD.

Seventy-six OCD patients were medicated, with $n = 62$ taking selective serotonin reuptake inhibitors (SSRIs) and $n = 33$ receiving other antidepressants over the previous 4 weeks. Sixty-five patients were medication-naïve. Furthermore, the majority of patients had one or more comorbid Axis I disorders, with major depression being the most common comorbidity ($n = 37$ current episode; $n = 66$ remitted). Other current comorbidities included: panic disorder ($n = 3$ with agoraphobia; $n = 5$ without agoraphobia), social phobia ($n = 13$), specific phobia ($n = 12$), generalized anxiety disorder ($n = 7$), posttraumatic stress disorder ($n = 6$), attention deficit/hyperactivity disorder ($n = 3$), anorexia nervosa ($n = 1$), binge eating disorder ($n = 2$), tic disorder ($n = 13$), skin picking disorder ($n = 10$), hypochondria ($n = 5$), body dysmorphic disorder ($n = 2$), hoarding disorder ($n = 4$), pain disorder ($n = 1$), and unspecified somatoform disorder ($n = 6$).

The severity of OCD symptoms was evaluated with the German versions of the Yale-Brown Obsessive-Compulsive Scale [Y-BOCS; (40, 41)] and the Obsessive-Compulsive Inventory-Revised [OCI-R; (42, 43)]. Symptom dimensions were measured via the Y-BOCS Symptom Checklist [Y-BOCS CL; (40)]. The Montgomery Asberg Depression Rating Scale [MADRS;(44, 45)] and the Beck Depression Inventory-II [BDI-II; (46, 47)] were employed to assess the severity of current depressive symptoms. To account for potential effects of state anxiety, the State-Trait Anxiety Inventory [STAI; (48, 49)] was administered. Harm avoidance was assessed using the German version of the Temperament and Character Inventory [TCI; (50, 51)]. All participants had normal or corrected-to-normal vision and were free of any neurological disease (lifetime).

TABLE 1 | Demographic and clinical characteristics of patients with OCD, unaffected first-degree relatives and healthy control subjects.

	Patients with OCD	Unaffected first-degree relatives	Healthy control subjects	Statistic	*p*
N	169	100	183		
Mean age, years (*SD*)	32.69 (10.44) [18–64]	46.55 (13.73) [18–67]	34.20 (12.70) [18–64]	$F(2, 449) = 45.72$	<0.001
Gender, % male	43.2	31.0	37.7	$X^2(2) = 4.00$	0.14
Education (*SD*)[a]	4.90 (1.81) [1–7]	4.78 (2.00) [1–7]	5.17 (1.60) [1–7]	$F(2, 447) = 1.88$	0.15
Mean OCI-R score (*SD*)	27.76 (12.22) [5–64]	7.11 (6.76) [0–35]	4.57 (4.51) [0–22]	$F_{(2, 449)} = 357.15$	<0.001
Mean BDI-II score (*SD*)	18.46 (10.60) [0–45]	5.88 (6.96) [0–28]	2.96 (3.64) [0–18]	$F_{(2, 449)} = 195.59$	<0.001
Mean state anxiety score (*SD*)	42.32 (9.69) [22–72]	33.80 (7.52) [22–60]	31.39 (5.97) [20–52]	$F_{(2, 448)} = 89.35$	<0.001
Mean harm avoidance score (*SD*)	22.34 (6.65) [3–35]	14.61 (6.51) [1–31]	10.77 (5.22) [0–25]	$F_{(2, 445)} = 160.33$	<0.001
Mean MADRS score (*SD*)[b]	11.60 (8.60) [0–41]				
Mean Y-BOCS score (*SD*)[b]	22.03 (6.71) [0–35][c]				
Mean age of onset (*SD*)[b]	20.93 (11.01) [3–59]				

The range of scores is indicated in brackets. BDI-II, Beck Depression Inventory-II; MADRS, Montgomery Asberg Depression Rating Scale; OCD, obsessive-compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] *Education was assessed on a scale from 1 to 7.*

[b] *MADRS, Y-BOCS and age of onset were only assessed in patients.*

[c] *One patient had severe OCD in the past, but was fully remitted at the time of testing.*

Written informed consent was obtained and participants were compensated for their time. The study was in accordance with the revised Declaration of Helsinki and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Clinic Bonn.

Eye Movement Recordings

Testing took place in a quiet, dimly lit room. Participants were seated comfortably in front of a 22-inch liquid crystal display (LCD) monitor (Viewsonic; height: 29.5 cm; width: 47.5 cm; resolution: 1,680 × 1,050 pixels; 60 Hz refresh rate) with a distance from eyes to screen of 70 cm. A chin rest was used to minimize head movements. At the Bonn assessment site, movements of the right eye were recorded using the EyeLink 1,000 system (SR Research, Mississauga, Ontario, Canada) at a sampling frequency of 1,000 Hz, whereas in Berlin, eye movements were recorded using the EyeLink II system (SR Research, Mississauga, Ontario, Canada) at a sampling rate of 250 Hz. Before the task started, the eye-tracker was calibrated with a five-point calibration task (0°, horizontal ± 13.3°, vertical ± 9.3°).

Saccade Tasks

The saccade task was programmed with SR Research's Experiment Builder (version 1.10.1241). Pro- and antisaccades were evaluated via a blocked task design, with each block comprising 60 trials. At the beginning of each trial, participants were required to look at a central fixation cue (width and height: 0.46°), which remained on screen throughout each trial (overlap paradigm). After a random interval of 1,000–2,000 ms, a target stimulus (width and height: 0.46°) appeared in either the left or the right periphery at an angle of 16° and remained there for 800 ms. In the prosaccade block, subjects were instructed to make a saccade toward the peripheral target as fast and accurately as possible, whereas in the antisaccade block, subjects were required to make a saccade in the direction opposite of the target. Five practice trials were presented before each block in which the experimenter ensured that the subject had understood the instructions correctly. All stimuli were presented on a black background. Pro- and antisaccade blocks appeared in a fixed order as the strong main effect of task (latency of antisaccades > prosaccades) is well-established throughout the literature (52). Tasks were part of a larger oculomotor battery with additional tasks, of which the results were already (53, 54) and will be reported elsewhere.

Eye Movement Analysis

Saccades were identified according to SR Research's saccade detection algorithm (Data Viewer, version 1.11.900) and individually verified by a rater. Criteria for the identification of saccades were a velocity > 30°/s, an acceleration > 8,000°/s^2, a minimum amplitude of 1° and a minimum latency to the peripheral stimulus of 80 ms (55). Trials including oculomotor events, i.e., saccades or blinks, <100 ms before stimulus onset were also excluded to ensure that subjects did not miss the onset of stimulus presentation [e.g., (56); on average 3.5% of trials were excluded in OCD patients, 4.6% in relatives and 2.8% in controls due to anticipatory eye movements]. Furthermore, trials were discarded if the gaze position at saccade onset deviated more than 2.3° (100 pixels) from the fixation stimulus position. Six subjects, who performed <15 valid trials for either of the tasks, were excluded from the analyses (57). For each subject, mean latencies and ISV of correctly performed pro- and antisaccades were calculated. Error rates were square-root transformed in order to obtain normal distribution and further subdivided into errors with express latency (≤130 ms) and regular latency [>130 ms; (55, 58)].

Statistical Analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Release 23.0 (SPSS Inc., Chicago, IL, USA). To test the hypothesis of impaired antisaccade performance in OCD patients, we conducted 2 × 2 analyses of variance (ANOVA) with group as the between-subjects factor (OCD patients vs. healthy comparison subjects) and task condition (prosaccades vs. antisaccades) as the within-subjects factor. Two distinct ANOVAs were carried out with mean saccade latency and ISV, i.e., *SD*, of saccades as dependent variables. In order to disentangle the interaction effects, *post-hoc t*-tests were conducted. Group differences in error rates were investigated with one-way ANOVAs. Results from these analyses were included in the combined meta-analysis, as described in section Statistical Methods.

Antisaccade performance of unaffected relatives was assessed via similar analyses. As relatives were significantly older than OCD patients and healthy volunteers, and age had a strong impact on saccade performance, it was included as a covariate for all ANOVAs that comprised relatives. To further support these results, additional analyses were conducted comparing unaffected relatives and a subsample of age-matched control subjects ($n = 96$).

Associations with specific OCD symptom dimensions were investigated using the Y-BOCS CL. Following the procedure established in previous studies (24, 59), the 13 main categories of the Y-BOCS CL were coded as 1 if the patient reported having experienced at least one symptom of the respective category. Otherwise, the category was coded as 0. These binary variables were then fed into an exploratory principal component analysis (PCA) with varimax rotation. Factors were extracted based on the Kaiser-Guttmann criterion, i.e., eigenvalue > 1. For each OCD patient, factor scores were exported for utility in further analyses.

Pearson's correlation coefficients were computed in order to explore relationships between mean saccade latencies and ISV, antisaccade error rates and continuous clinical variables. Group differences in demographic and clinical characteristics were tested using ANOVAs and Fisher's chi-square test was utilized to compare sex ratios across groups. We also performed exploratory ANOVAs using medication [medication-naïve ($n = 65$) vs. any psychoactive medication within the past 4 weeks ($n = 81$) vs. previous psychoactive medication but not within the past 4 weeks ($n = 23$)] and depressive comorbidity [current episode of major depression ($n = 37$) vs. remitted major depression ($n = 66$) vs. no lifetime diagnosis of major depression ($n = 64$)] as the between-subjects factor in OCD patients. Moreover,

analyses were rerun excluding all OCD patients with current comorbid anxiety disorders, i.e., specific phobia, social phobia, panic disorder with/without agoraphobia and generalized anxiety disorder ($n = 35$). To investigate whether significant group differences in antisaccade performance were driven by increased levels of anxiety, correlations with state anxiety and harm avoidance were computed. The alpha level was set to 0.05 for all primary statistical analyses. In the correlation analysis evaluating OCD symptom dimensions, Bonferroni correction was applied to account for multiple comparisons.

Meta-Analysis

Study Selection for Meta-Analysis

We conducted a systematic, comprehensive literature search of the PubMed database for relevant, full-length articles published up to the 30th April 2017 with the following search expressions: ("obsessive-compulsive disorder" OR "OCD" OR "obsessive-compulsive") AND ("antisaccade" OR "anti-saccade" OR "saccade" OR "saccadic eye movement"). Publication reference lists of identified articles were searched as well. Only original research articles written in English and published in peer-reviewed journals were considered. The included studies were strictly those which made use of either video-oculography or electrooculography (EOG) to assess antisaccades. Studies employing complex picture stimuli as peripheral targets instead of simple cues were excluded. All studies were required to feature one group of individuals classified as having OCD based on a standardized clinical interview and one group of healthy (i.e., screened for the absence of a psychiatric or neurologic diseases) control subjects. Studies examining patient populations overlapping with previous publications were excluded. A flowchart showing the procedure of study selection according to the aforementioned criteria and PRISMA guidelines (60) is presented in **Figure 1**.

Data Extraction

From each study, means and *SD*s or results from statistical tests (t, F, and p statistics) were extracted to compute the standardized mean difference (Cohen's d) in antisaccade latencies and error rates. As only one study reported ISV of antisaccade latencies and no study has investigated express and regular errors thus far, these measures could not be considered for meta-analysis. Additionally, we extracted the year of publication of each study, samples size, sex ratio as well as means and *SD*s of age and verbal intelligence quotient (IQ; or measures of education). If available, information on symptom severity as evaluated by Y-BOCS, the proportion of patients receiving psychotropic medication, the proportion of patients with comorbid depressive disorders, depressive symptom severity (e.g., according to the Hamilton Depression Rating Scale; HAM-D), age of OCD onset and task characteristics were extracted, too. The variables recorded were cross-verified by two researchers.

One study did not describe the main effect of group on antisaccade error rates but only the group × target amplitude interaction (20). As it was not possible to derive mean values and *SD*s across all three target amplitude conditions (8, 16, and 24°) from the information given, only results from the 16° condition were included in the meta-analysis. Similarly, McDowell and Clementz (19) reported statistics separately for each fixation cue condition (step, gap, overlap). For the sake of comparability with the present study's findings, data from the overlap condition were included in the meta-analysis. Furthermore, Agam et al. (14) reported antisaccade data from the same sample once acquired during electroencephalography (EEG) and once during functional magnetic resonance imaging (fMRI). As the EEG session was performed first, included more antisaccade trials and was presumably more comparable to the setup of the other studies, antisaccade data acquired during EEG were part of the present meta-analysis. Data from Maruff et al. (18) were read off figures as precisely as possible because the exact values could

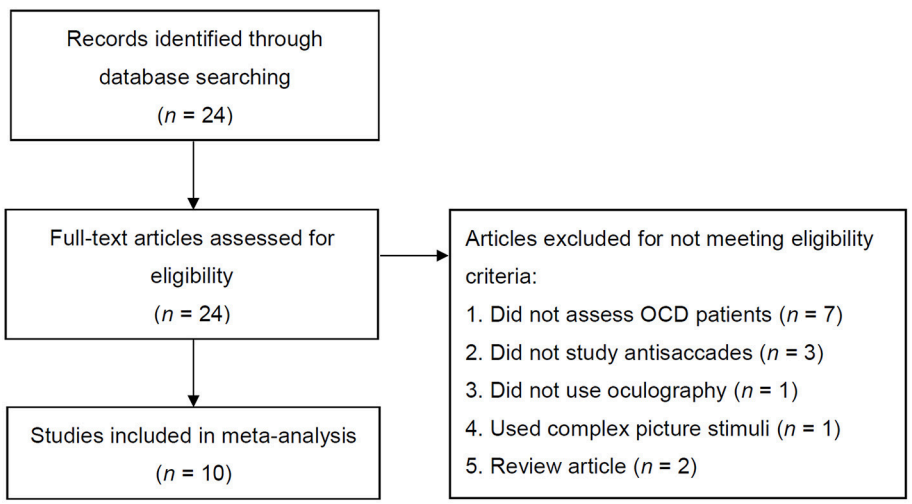

FIGURE 1 | Flowchart showing the process of article selection. OCD, obsessive-compulsive disorder.

not be retrieved. Finally, two studies used square-root (17) and logit transformations (14), respectively, in order to obtain normal distributions of error rates. In these cases, effect sizes derived from analyses of the transformed values were featured in the meta-analysis, instead of raw values.

Statistical Methods

Meta-analyses were conducted using the R-based software OpenMetaAnalyst (61). Effect sizes of outcome variables were estimated by computing the standardized mean difference (*SMD*), which is a measure of effect size calculated by subtracting the control group's mean from the OCD group's mean and dividing by the pooled *SD*. For each outcome measure within a study, i.e., antisaccade error rates and latencies, separate effect sizes were computed. Positive effect sizes indicated worse oculomotor functioning, i.e., higher error rates or longer latencies, in the OCD group relative to the control group, whereas negative effect sizes suggested better performance in OCD patients. With few exceptions, effect sizes were calculated directly from means and *SD*s reported in studies. When this information was not available, results of other statistical tests (e.g., t and F statistics) were consulted to calculate effect size (62). A weighted-average effect size was then computed for each outcome variable using the Hedges-Olkin random-effects method (63). To determine whether effect sizes were consistent across studies, we calculated the homogeneity statistics, Q and I^2, where $I^2 = [(Q\text{-df})/Q] \times 100\%$, which describes the proportion of the variability in effect estimates that emanated from heterogeneity rather than sampling error.

Moreover, several meta-regressions were performed with mean age, proportion of males, proportion of medicated patients, mean Y-BOCS scores, task design (gap, step, overlap), number of trials, target amplitude and mean cue latency as moderators in order to investigate systematic influences of sample and task characteristics on antisaccade error rates and latencies.

RESULTS

Empirical Study

Effects of Task, Age and Study Site

Mean saccade latencies were significantly faster for the prosaccade task than the antisaccade task [$F_{(1, 451)} = 1426.64$, $p < 0.001$, $\eta^2 = 0.76$, 95% CI (0.73, 0.79)]. A main effect of age indicated that saccade latencies rose with age [$F_{(1, 450)} = 58.65$, $p < 0.001$, $\eta^2 = 0.12$, 95% CI (0.07, 0.17)]. Likewise, analysis of ISV of saccade latencies revealed a main effect of task type [$F_{(1, 451)} = 135.08$, $p < 0.001$, $\eta^2 = 0.23$, 95% CI (0.17, 0.29)] with smaller ISV for the prosaccade task than the antisaccade task. ISV of saccade latencies significantly increased with age, as well [$F_{(1, 450)} = 25.59$, $p < 0.001$, $\eta^2 = 0.05$, 95% CI (0.02, 0.10)]. Importantly, there was no effect of study site on any of the examined saccade variables (all $p > 0.05$).

Saccade Performance in OCD Patients and Healthy Comparison Subjects

Comparing mean saccade latencies between OCD patients and healthy controls yielded a significant group-by-task interaction [$F_{(1, 350)} = 10.76$, $p = 0.001$, $\eta^2 = 0.03$, 95% CI (0.005, 0.07)]. In particular, patients had longer antisaccade latencies [$t_{(350)} = 2.05$, $p = 0.042$, $d = 0.22$, 95% CI (0.01, 0.43)], while there was no difference in prosaccade latencies between patients and controls [$t_{(329.08)} = -1.32$, $p = 0.19$, $d = 0.14$, 95% CI (−0.07, 0.01)]. Analysis of ISV yielded a significant effect of group [$F_{(1, 350)} = 10.42$, $p = 0.001$, $\eta^2 = 0.03$, 95% CI (0.004, 0.07)] along with a significant group-by-task interaction [$F_{(1, 350)} = 14.74$, $p < 0.001$, $\eta^2 = 0.04$, 95% CI (0.01, 0.09)] indicative of OCD patients exhibiting higher ISV in the antisaccade task compared to healthy controls [$t_{(315.39)} = 4.06$, $p < 0.001$, $d = 0.44$, 95% CI (0.23, 0.65); **Figure 2**], while ISV of prosaccades did not differ between groups [$t_{(350)} = 1.01$, $p = 0.31$, $d = 0.11$, 95% CI (−0.10, 0.32)]. Furthermore, patients made significantly more errors in the antisaccade task than controls [$t_{(322.47)} = 2.09$, $p = 0.037$, $d = 0.22$, 95% CI (0.01, 0.43)]. This effect was driven by express errors [$t_{(309.94)} = 2.49$, $p = 0.013$, $d = 0.27$, 95% CI (0.06, 0.48)], as groups did not differ significantly regarding regular errors [$t_{(350)} = 1.17$, $p = 0.24$, $d = 0.12$, 95% CI (−0.08, 0.33); **Figure 3**].

Saccade Performance in Unaffected Relatives

Unaffected relatives did not differ from control subjects with regards to pro- and antisaccade latencies ($p > 0.05$ for both the main effect of group and the group-by-task interaction). However, relatives exhibited significantly higher ISV of latencies across tasks [$F_{(1, 280)} = 4.62$, $p = 0.033$, $\eta^2 = 0.02$, 95% CI (0.0, 0.06); **Figure 2**]. While the group difference in overall error rate did not reach significance [$F_{(1, 280)} = 1.40$, $p = 0.24$, $\eta^2 = 0.005$, 95% CI (0.0, 0.03)], separate analyses of express and regular errors suggested a significant effect of group on the rate of express

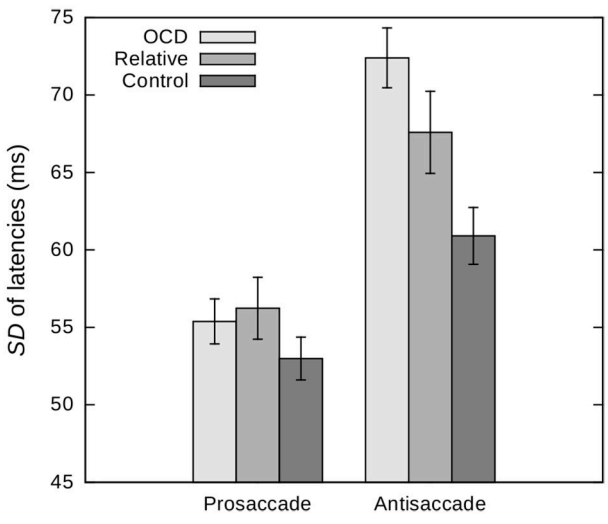

FIGURE 2 | Intra-subject variability, i.e., *SD*s, of pro- and antisaccade latencies in patients with obsessive-compulsive disorder (OCD), unaffected first-degree relatives and healthy control subjects. Age is included as a covariate and values are depicted for a mean age of 36.37 years. Error bars indicate standard errors. The effect of group and the group by task interaction are significant at $p = 0.002$ and $p = 0.001$, respectively.

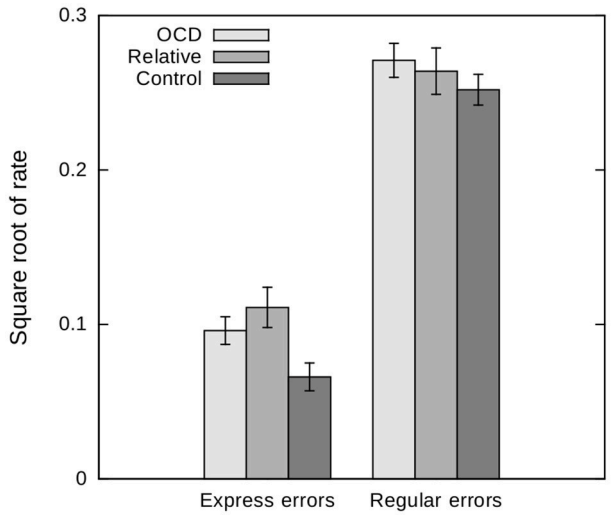

FIGURE 3 | Express and regular error rates in the antisaccade task in patients with obsessive-compulsive disorder (OCD), unaffected first-degree relatives and healthy control subjects. Age is included as a covariate and values are depicted for a mean age of 36.37 years. Error bars indicate standard errors. Groups differ significantly regarding express errors ($p = 0.007$), but not regarding regular errors ($p = 0.45$).

errors [$F_{(1, 280)} = 7.71$, $p = 0.006$, $\eta^2 = 0.03$, 95% CI (0.002, 0.07)] but not on the rate of regular errors [$F_{(1, 280)} = 0.29$, $p = 0.59$, $\eta^2 = 0.001$, 95% CI (0.0, 0.02); **Figure 3**]. Relatives did not significantly differ from OCD patients across all measures (all $p > 0.05$).

These results were supported by additional analyses comparing unaffected relatives to a subsample of age-matched controls ($n = 96$). Groups did not differ with regards to pro- and antisaccade latencies ($p > 0.05$ for both the main effect of group and the group-by-task interaction), but relatives exhibited significantly higher ISV of latencies across tasks [$F_{(1, 194)} = 6.33$, $p = 0.013$, $\eta^2 = 0.03$, 95% CI (0.0, 0.09)]. Again, the group difference in overall error rate did not reach significance [$t_{(194)} = 1.84$, $p = 0.07$, $d = 0.26$, 95% CI (−0.02, 0.54)], while separate analyses of express and regular errors yielded a significant effect of group on the rate of express errors [$t_{(186.88)} = 2.93$, $p = 0.004$, $d = 0.42$, 95% CI (0.14, 0.70)] but not on the rate of regular errors [$t_{(194)} = 1.32$, $p = 0.19$, $d = 0.19$, 95% CI (−0.09, 0.47)].

Effects of Medication, Depressive Comorbidity, and OCD Severity

Analyses of OCD patients with current, previous and no history of major depression did not yield any significant effects (all $p > 0.05$). Moreover, patients taking psychoactive medication did not differ from previously and never-medicated patients regarding antisaccade latencies, ISV and error rates (all $p > 0.05$). There were no significant associations between symptom severity as assessed by Y-BOCS or any of the saccade performance measures, either (all $p > 0.05$).

Effects of Anxiety

Excluding OCD patients with current comorbid anxiety disorders did not alter the results substantially. Furthermore, there were no significant correlations between state anxiety and antisaccade performance in either OCD patients, unaffected relatives, or healthy controls (all $p > 0.05$). While we did not observe any associations between harm avoidance and antisaccade parameters in OCD patients and healthy controls (all $p > 0.05$), there was a significant positive correlation between harm avoidance and antisaccade error rate ($r = 0.23$, $p = 0.020$) in relatives, which was particularly pronounced with regards to express errors ($r = 0.30$, $p = 0.002$).

Symptom Dimensions

PCA of Y-BOCS CL items yielded five factors representing the dimensions of ordering/symmetry/counting, checking/intrusive thoughts (aggression, religion, body), washing/contamination, hoarding and repeating/sexual obsessions. After controlling for multiple comparisons, none of the correlations between symptom dimensions and antisaccade performance parameters reached significance.

Meta-Analysis

Meta-Analysis of Previous Studies

After standardized study selection (**Figure 1**), 10 studies were included in the meta-analysis with a total of 189 OCD patients and 204 control subjects. Samples and task characteristics are presented in **Tables 2**, **3**.

Meta-analysis of antisaccade error rates yielded a weighted-average *SMD* of 0.55 [95% CI (0.28, 0.81), $p < 0.001$]. According to the Q and I^2 statistics, results across the studies were moderately, though not significantly, heterogeneous [$Q_{(9)} = 12.71$, $I^2 = 35.32\%$, $p = 0.18$]. As indicated by the meta-regressions, there was no significant impact of age ($b = 0.012$, $p = 0.55$), gender ($b = 0.002$, $p = 0.74$), medication ($b = 0.45$, $p = 0.24$) and Y-BOCS score ($b = 0.024$, $p = 0.67$). In terms of task characteristics, there was no effect of task design ($p = 0.95$), number of trials ($b = 0.001$, $p = 0.60$), target amplitude ($b = -0.015$, $p = 0.68$) and mean cue latency ($b = 0.000$, $p = 0.095$).

Meta-analysis of antisaccade latencies yielded a similar *SMD* of 0.56, but the effect did not reach significance [95% CI (−0.06, 1.17), $p = 0.075$] as considerable statistical heterogeneity was observed [$Q_{(8)} = 36.12$, $I^2 = 87.26\%$, $p < 0.001$]. Meta-regressions using mean age ($b = 0.067$, $p = 0.078$), proportion of males ($b = -0.006$, $p = 0.67$), proportion of medicated patients ($b = -0.17$, $p = 0.83$) and mean Y-BOCS scores ($b = 0.16$, $p = 0.20$) as moderators did not yield any significant effects on *SMD*. Furthermore, there was no effect of task design ($p = 0.95$), number of trials ($b = -0.001$, $p = 0.80$), target amplitude ($b = 0.006$, $p = 0.94$) and mean cue latency ($b = 0.001$, $p = 0.16$).

Meta-Analysis of Previous and the Present Empirical Study

Including the present empirical study in the meta-analysis of antisaccade error rates yielded a weighted-average *SMD* of 0.48 [95% CI (0.24, 0.72), $p < 0.001$; **Figure 4A**]. Again, we noted

TABLE 2 | Sample characteristics of the 10 studies included in the meta-analysis.

Author (year)	*n* of OCD group	*n* of control group	Mean age (*SD*) of OCD group	Mean age (*SD*) of control group	% male in OCD group	% male in control group	Mean estimated verbal IQ (*SD*) of OCD group	Mean estimated verbal IQ (*SD*) of control group	Depressive comorbidity	Mean depressive symptom severity (*SD*)	Mean OCD symptom severity as assessed by Y-BOCS (*SD*)	Mean age of OCD onset (*SD*)	Medication	OCD symptom dimensions
(22)	11	14	39 (7)	38 (10)	45.5 or 54.4 %[a]	42.9 or 50.0 %[a]	similar education		–	–	24.4 (4.5)	–	$n = 1$ none, $n = 10$ AD	–
(19)	12	12	32.7 (10.4)	37.0 (15.3)	58 %	42 %	–	–	–	HAM-D: median = 8	O: median = 11 C: median = 11	–	$n = 4$ none, $n = 8$ psychotropic medication	–
(20)	12	12	30.1 (9.4)	30.2 (9.0)	50.0 %	50.0 %	similar socioeconomic status		$n = 1$ dysthymia	HAM-D: median = 7	O: median = 11 C: median = 10	21.0 (9.2)	all medication-free	–
(18)	12	12	47.0 (8.5)	46.0 (9.9)	41.7 %	41.7 %	similar education		–	HAM-D: 9.0 (4.4)	24.2 (10.3)	20.7 (13.4)	$n = 3$ none, $n = 9$ AD	–
(21)	22	24	34.2 (11.2)	31.0 (6.3)	59.1 %	62.5 %	–	–	$n = 1$ MDD, $n = 7$ dysthymia	–	20.1 (7.7)	–	$n = 2$ none, $n = 20$ AD	–
(23)	14	14	29.1 (7.2)	28.4 (6.28)	64.3 %	64.3 %	–	–	all comorbidity-free	HAM-D: 8.0 (4.3)	23.7 (3.8)	$n = 8$ juvenile, $n = 6$ adult	all psychotropic-naïve	–
(16)	30	30	32.3 (9.8)	32.8 (9.2)	36.7 %	36.7 %	105.4 (9.6)	106.9 (8.8)	–	MADRS: 4.9 (6.2)	18.0 (7.0)	18.1	$n = 15$ none, $n =$15 AD	mixed (OCI-R)
(17)	21	21	38.9 (6.9)	41.2 (13.0)	47.6 %	38.1 %	114.7 (12.8)	116.6 (12.4)	$0 \leq n \leq 8$ MDD[b]	BDI: 11.86 (8.71)	17.2 (8.3)	–	$13 \leq n \leq 21$ AD[b]	mixed (Y-BOCS Checklist)
(14)	21	20	33 (11)	33 (11)	38.1 %	55.0 %	110 (11)	113 (6)	$n = 1$ MDD, $n = 4$ dysthymia	BDI-II: 13 (9)	23 (5)	–	$n =$14 none, $n = 6$ AD, $n = 1$ AD + memantine	$n = 10$ washing, $n = 9$ checking + obsessions, $n = 2$ symmetry
(15)	34	45	23.2 (3.4)	23.2 (1.3)	100.0 %	100.0 %	–	–	–	–	range = 14–33	–	$n = 6$ none, $n = 16$ AD, $n = 7$ AD + AP, $n = 3$ AD + MS, $n =$ 1 AD + AP + MS, $n = 1$ buspirone	–

AD, antidepressants; AP, antipsychotics; BDI, Beck Depression Inventory; C, compulsions subscale of the Y-BOCS; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MS, mood stabilizers; O, obsessions subscale of the Y-BOCS; OCD, obsessive-compulsive disorder; OCI-R, Obsessive-Compulsive Inventory-Revised; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale. Hyphens indicate that the specific characteristic was not reported.

[a] *The information given in the main text and figures is divergent.*

[b] *Characteristics were only available for the full sample, but not for the subsample which completed the antisaccade task.*

TABLE 3 | Task characteristics and results of the 10 studies included in the meta-analysis.

Author (year)	Task design	*n* of trials	Target amplitude	Cue latencies	Results: mean latencies	Results: error rates	Results: *SD* of latencies
(22)	step	10–16	∼10°	–	–	OCD > CON	–
(19)	step, gap, or 200 ms overlap	120	10, or 20°	2,000–2,500 ms	OCD > CON	OCD = CON	–
(20)	step	36	8, 16, or 24°	1,500–2,500 ms	OCD = CON	OCD > CON (8°) OCD = CON (16°) OCD = CON (24°)	–
(18)	step	106	10, or 15°	2,000–2,500 ms	OCD > CON	OCD = CON	–
(21)	step	20	12°	700, 1,000, or 1,300 ms	OCD = CON	OCD = CON	–
(23)	200 ms gap	50	7°	1,000 ms	OCD > CON	OCD = CON	–
(16)	overlap	40	–	1,000–2,000 ms	OCD = CON	OCD = CON	–
(17)	200 ms overlap	50	16°	1,500, 2,000, 2,500, or 3,000 ms	OCD > CON (only interaction term with prosaccades)	OCD > CON	–
(14)	200 ms gap; 50% trials with distractor; 40% without distractor, 10% fake-hard; twice: during fMRI and EEG	384 (EEG) 512 (fMRI)	10°	2,000 ms	OCD = CON (EEG) OCD = CON (fMRI)	OCD = CON (EEG) OCD > CON (fMRI)	–
(15)	step	90	2–10° (1° intervals)	1,000–2,000 ms	OCD = CON	OCD > CON	OCD > CON

CON, healthy control subjects; OCD, obsessive-compulsive disorder; SD, standard deviation.
Hyphens indicate that the specific characteristic was not reported.

moderate, though non-significant, heterogeneity across studies [$Q_{(9)} = 17.22$, $I^2 = 45.03\%$, $p = 0.070$]. As indicated by the meta-regressions, there was no significant effect of age ($b = 0.012$, $p = 0.56$), gender ($b = 0.005$, $p = 0.34$), medication ($b = 0.55$, $p = 0.15$) and Y-BOCS score ($b = 0.010$, $p = 0.86$). While there was no impact of task design ($p = 0.84$), number of trials ($b = 0.001$, $p = 0.48$) and target amplitude ($b = -0.04$, $p = 0.050$) on *SMD*, the effect of mean cue latency ($b = 0.000$, $p = 0.035$) reached significance. Specifically, longer cue latencies were associated with greater *SMD*s.

Meta-analysis of antisaccade latencies yielded a weighted-average *SMD* of 0.51 [95% CI (−0.04, 1.06), $p = 0.069$; **Figure 4B**]. The Q and I^2 statistics indicate that results across studies were significantly heterogeneous [$Q_{(9)} = 37.14$, $I^2 = 90.20\%$, $p < 0.001$]. Meta-regressions utilizing mean age ($b = 0.065$, $p = 0.072$), proportion of males ($b = -0.003$, $p = 0.77$), proportion of medicated patients ($b = -0.18$, $p = 0.80$) and mean Y-BOCS scores ($b = 0.14$, $p = 0.20$) as moderators did not yield any significant effects on *SMD*. With respect to task characteristics, there was no effect of task design ($p = 0.98$), number of trials ($b = -0.000$, $p = 0.82$), target amplitude ($b = -0.008$, $p = 0.91$) and mean cue latency ($b = 0.001$, $p = 0.12$).

DISCUSSION

The present study serves as an extensive investigation of antisaccade performance in OCD patients and their unaffected first-degree relatives. Convergent findings from meta-analysis and a large empirical study indicate that patients with OCD exhibit significantly increased error rates in the antisaccade task while response latencies are not consistently elongated. Whereas effect sizes for error rates and mean latencies appear to be just moderate, we observed pronounced group differences with regards to ISV of antisaccade latencies in OCD patients as well as in unaffected relatives, providing the first evidence for a potential endophenotype of OCD. Furthermore, detailed analyses of error rates indicate that both patients and first-degree relatives exhibit more express errors in the antisaccade task than healthy controls.

Our findings highlight that antisaccade deficits in OCD are substantial, but only of moderate effect size and limited by inconsistencies across studies. The meta-analysis of 10 studies showed that patients with OCD feature a significantly increased antisaccade error rate compared to matched healthy controls. With regards to antisaccade latencies, however, the group difference did not reach significance as there was large heterogeneity across studies. As indicated by meta-regression, age, gender, medication status and OCD severity did not contribute to the variability in effect sizes, suggesting that OCD patients' deficits in the antisaccade task are not moderated by demographic variables. This observation is in agreement with the meta-analyses of cognitive function in OCD (64, 65) and the absence of associations between patients' medication status, depressive comorbidity, OCD severity and oculomotor performance in our empirical data. Still, other clinical variables which are less state-dependent and more strongly related to the genetic underpinnings of OCD, such as age of onset (66) and symptom dimensions (67), could not be analyzed via meta-regressions based on the small number of studies reporting relevant information. With respect to our empirical investigation,

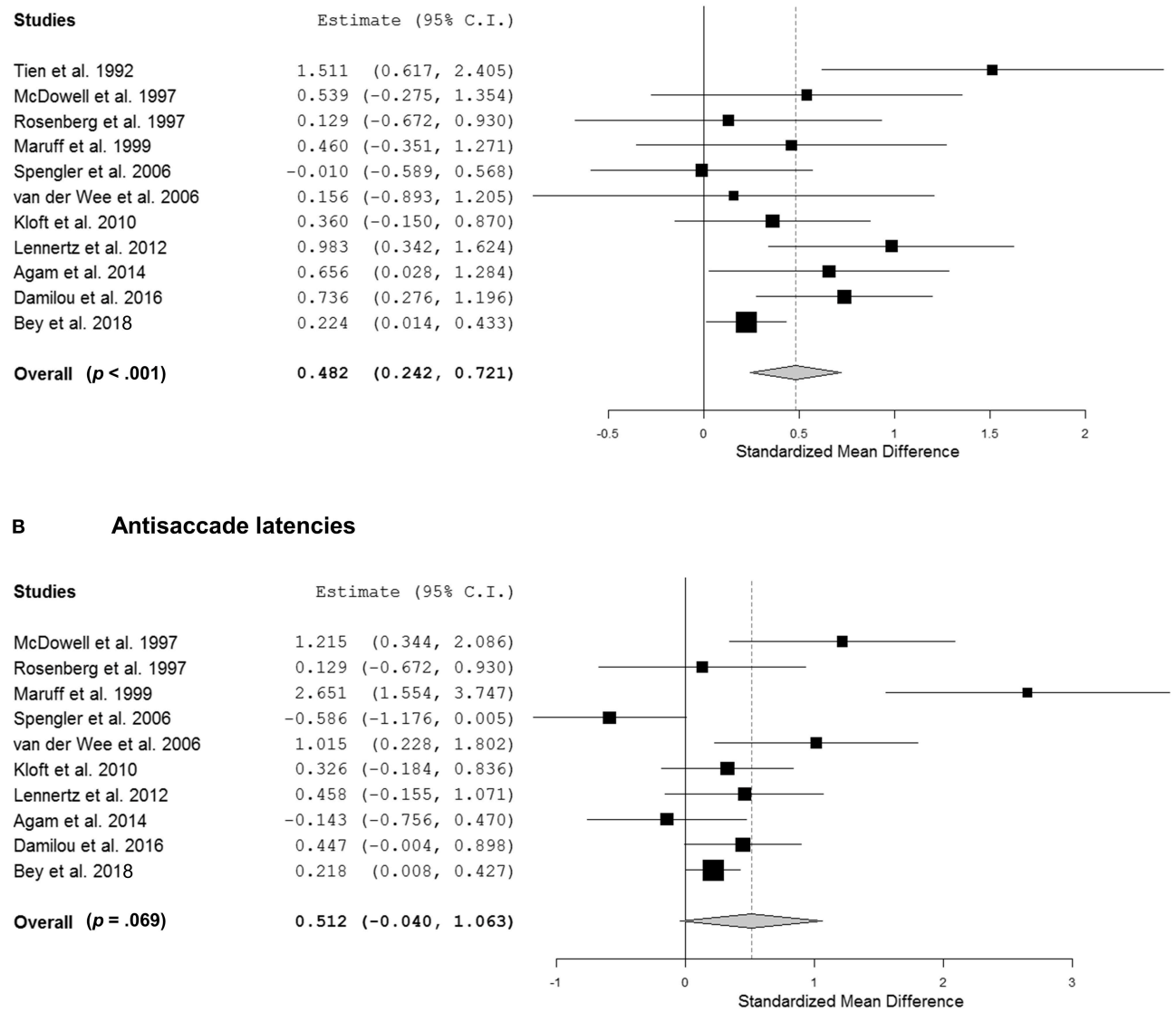

FIGURE 4 | (A) Forest plot showing effect sizes for antisaccade error rates in patients with obsessive-compulsive disorder (OCD) as compared to healthy control subjects. Higher values indicate higher error rates in patients. **(B)** Forest plot portraying the effect sizes for antisaccade latencies in patients with OCD as compared to healthy control subjects. Higher values indicate longer latencies in patients.

however, we did not observe any significant correlations between OCD symptom dimensions and antisaccade performance after controlling for multiple comparisons.

While the majority of task characteristics did not affect *SMD* as was indicated by the meta-regressions, the effect of mean cue latency reached significance when the present empirical study was included. Accordingly, longer mean cue latencies were associated with greater group differences in error rates. Though longer cue latencies are not generally associated with higher error rates or an increased frequency of express saccades, OCD patients and controls might be differentially affected by the manipulation of cue latencies, resulting in a growing group difference.

Our empirical data indicate that the increased antisaccade error rates in OCD patients are primarily driven by express latency errors. As reviewed by Coe and Munoz (29), express and regular errors arise from failures of different forms of suppression mechanisms, which can be investigated via neurophysiological experiments in macaques. At the start of an antisaccade trial, pre-emptive top-down inhibition of saccade-generating neurons in the frontal eye fields and the intermediate layers of the superior colliculus (SCi) must be present before the stimulus appears in order to prevent express errors. After the stimulus' appearance, voluntary antisaccade commands must compete with, and override, automated visually initiated saccade commands to

prevent longer latency errors. Potential sources of pre-stimulus inhibition comprise fixation neurons within the SCi, which are tonically active during visual fixation and cease firing during the execution of saccades (68). Hence, the inhibition of neurons in the SCi prior to stimulus elicitation is crucial to preventing the initial visual transient response from triggering a direction error (29). The CSTC model of OCD is in accordance with the observed excess in express errors. Specifically, imbalances between the direct and indirect CSTC pathways may not only result in a reduced inhibition of the thalamus, but may also contribute to a diminished inhibition of the SCi during the antisaccade task, which may hence cease firing more easily and facilitate the execution of quick, reflexive saccades toward the target. Notably, oculomotor regions of the frontal cortex and the basal ganglia also feature pre-stimulus activity, establishing a form of top-down inhibition that appears to be required for the inhibition of the SCi (29). A deficient transmission of inhibitory signals from frontal regions to the SCi via the CSTC circuitry may hence foster an increased frequency of express error rates. Evidence from neuroimaging indicates that both OCD patients and their unaffected relatives show aberrations in CSTC functional connectivity (69), which may serve as the basis for the increased express error rates we observed. In conclusion, our findings support the role of the antisaccade error rate as a potential endophenotype of OCD (17) and point to a more particular mechanism, i.e., early pre-stimulus inhibition of the SCi.

Aberrant CSTC function may also contribute to the increased ISV of correct antisaccade latencies. To our knowledge, this is the first study to demonstrate that ISV in antisaccade latencies constitutes a potential endophenotype of OCD. While increased *SD*s of antisaccade latencies have previously been described in OCD patients (15), unaffected first-degree relatives have not been evaluated thus far. In general, ISV in reaction times is most strongly observed in tasks that require executive control (70), indicating lapses of attention or cognitive control (71, 72). ISV of response times is sensitive to frontal dysfunction (73), increased in patients with schizophrenia (15) and also linked with the genetic risk of schizophrenia (74). Considering the strong genetic overlap between schizophrenia and OCD (75), endophenotypes of schizophrenia could prove informative for OCD, as well. In fact, endophenotypes have the potential to provide measures that are sensitive to multiple diagnostic constructs, and may aid the identification of shared pathomechanisms (76). Trans-diagnostic approaches of neurocognitive endophenotypes have been proposed, entailing instructive implications for the future classification of psychiatric disorders, genetics and therapeutics (77).

Twin studies of OCD and OCD-related traits yield heritability estimates of roughly 50% (78, 79), but until now, the identification of the specific genetic variants underlying this heritability has been difficult. Two genome-wide association studies (GWAS) studies and a recent meta-analysis of them did not provide evidence for genome-wide significant hits (80–82), possibly because of still insufficient sample sizes ($n = 2{,}688$ OCD patients and $n = 7{,}037$ controls). In recent years, this issue has been addressed by an endeavor to identify endophenotypes as potential vulnerability factors of OCD, which are presumably less genetically complex and hence more tractable to genetic analysis. According to established criteria, an endophenotype must: (a) be heritable; (b) be associated with the illness; (c) be independent of clinical state; (d) co-segregate with the illness within a family; and (e) represent reproducible measurements (32, 76). Antisaccade performance, specifically error rates, meets each of these criteria, rendering it a promising endophenotype of OCD: (a) with heritability estimates ranging from 42 to 61%, antisaccades have a strong genetic component (83–85); (b) antisaccade deficits have repeatedly been observed in patients with OCD; (c) OCD symptom severity is not correlated with antisaccade performance; (d) first-degree relatives of OCD patients exhibit worse performance than healthy subjects from the general population [(17); present study]; and (e) antisaccade error rates and the *SD*s of antisaccade latencies are sufficiently reliable (57, 86). Until now, antisaccade error rates are the most commonly researched outcome measure in the antisaccade task, while ISV of antisaccade latencies and express error rates have rarely been examined in endophenotype studies. Our findings highlight that OCD patients as well as their first-degree relatives exhibit prolonged *SD*s of antisaccade latencies and increased express error rates, independent of symptom severity. Further research investigating the genetic basis of these more detailed outcome measures is warranted. The genetic architecture of OCD appears to be highly polygenetic and primarily constituted of common variants (87, 88), with a SNP heritability that is among the highest of all psychiatric disorders (89). Future studies may look for associations between polygenic risk scores of OCD and antisaccade performance so as to assess shared genetic contributions. The identification of risk genes will contribute to the understanding of etiological mechanisms in OCD and may eventually point to new targets for medication.

In order to explore the potentially mediating role of anxiety, we assessed correlations between antisaccade performance, state anxiety, and harm avoidance, a personality trait that has previously been discussed as an endophenotype of OCD [(90) sample overlapping with the present sample; (91)]. While we did not observe any associations between state anxiety and antisaccade parameters within groups, there was a significant positive correlation between harm avoidance and antisaccade error rate in relatives, which was particularly pronounced with regards to express errors. Hence, the underperformances we observed in relatives of OCD patients appear to be driven by a shared vulnerability expressed in an anxious personality rather than by state anxiety. In accordance with the assumption of pleiotropy, the genetic risk for OCD that is presumably reflected in elevated scores of harm avoidance may at the same time contribute to elevated antisaccade error rates.

Concerning antisaccade latencies, the findings are less consistent. Although we observed slightly increased antisaccade latencies in OCD patients within our empirical sample, meta-analysis did not demonstrate a significant effect stemming from large heterogeneity. While the majority of studies examined antisaccade latencies without considering prosaccade latencies, our results indicate that using a repeated-measures model, including the saccade task as a between-subjects factor, yields

more pronounced group differences between OCD patients and controls. Whereas the mere comparison of antisaccade latencies barely reached significance, including prosaccade latencies in the model led to the observation of a strong group difference. Though groups did not differ significantly with respect to prosaccade latencies, the slightly faster prosaccades in patients contributed to the extensive group-by-saccade-task interaction effect. These results are in line with (17), who also observed a more pronounced effect when a repeated-measures approach was employed. Hence, disregarding prosaccades as a reference task may explain why the overall latency effect did not reach significance in the meta-analysis.

The present study is not without limitations. First, relatives were significantly older than patients and controls. In order to address this shortcoming, age was included as a covariate across all analyses comprising relatives, and additional analyses were conducted comparing relatives to an age-matched subsample of control subjects. Notably, patients and controls were well-matched with regards to age so the main analyses were not affected by this issue. Furthermore, the mean age of unaffected relatives lies well above the average age of onset of OCD symptoms, making it very unlikely that the effects are driven by subjects who will develop OCD later on. Second, a substantial number of patients was medicated with SSRI or other antidepressants. Though SSRI have been shown to influence functional brain networks (92), they do not seem to affect antisaccade performance (93). In line with this notion, we did not observe significant differences between medication-naïve, currently medicated and previously medicated OCD patients. Third, as many of the original studies appear to be underpowered, the power of the meta-analyses is likely also relatively low.

In summary, combining meta-analysis of previous findings with the assessment of a large and thoroughly characterized empirical sample allowed for an extensive examination of antisaccade performance in OCD while considering a large variety of covariates, including medication status, depressive comorbidity, comorbid anxiety disorders and OCD symptom dimensions. Our results indicate that antisaccade deficits in OCD are substantial, though of moderate effect size. Assessing more detailed parameters, such as express error rates and ISV of saccades, has shown to be informative, as we found first evidence that an increased ISV of antisaccade latencies and an elevated rate of express errors constitute potential endophenotypes of OCD.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

KB, LL, UE, NK, and MW contributed conception and design of the study; KB, LL, and IM programmed the saccade task; KB conducted the statistical analyses and wrote the first draft of the manuscript; KB, CK, LL, AR, JK, SH, and RG were involved in data-acquisition for this bi-centric study. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

1. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, et al. The cross national epidemiology of obsessive-compulsive disorder. *J Clin Psychiatry* (1994) 55:5–10.
2. Mataix-Cols D, Boman M, Monzani B, Rück C, Serlachius E, Långström N, et al. Population-based, multigenerational family clustering study of obsessive-compulsive disorder. *JAMA Psychiatry* (2013) 70:709–17. doi: 10.1001/jamapsychiatry.2013.3
3. Grabe HJ, Ruhrmann S, Ettelt S, Buhtz F, Hochrein A, Schulze-Rauschenbach S, et al. Familiality of obsessive-compulsive disorder in nonclinical and clinical subjects. *Am J Psychiatry* (2006) 163:1986–92. doi: 10.1176/ajp.2006.163.11.1986
4. Nestadt G, Samuels J, Riddle M, Bienvenu OJ, Liang KY, LaBuda M, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry* (2000) 57:358–63. doi: 10.1001/archpsyc.57.4.358
5. Pauls DL, Alsobrook, JP II, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. *Am J Psychiatry* (1995) 152:76–84. doi: 10.1176/ajp.152.1.76
6. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. (2008) 32:525–49. doi: 10.1016/j.neubiorev.2007.09.005
7. Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nat Rev Neurosci*. (2014) 15:410–24. doi: 10.1038/nrn3746
8. Saxena S, Bota RG, Brody AL. Brain-behavior relationships in obsessive-compulsive disorder. *Semin Clin Neuropsychiatry* (2001) 6:82–101. doi: 10.1053/scnp.2001.21833
9. Göttlich M, Krämer UM, Kordon A, Hohagen F, Zurowski B. Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. *Hum Brain Mapp*. (2014) 35:5617–32. doi: 10.1002/hbm.22574
10. van den Heuvel OA, van der Werf YD, Verhoef KM, de Wit S, Berendse HW, Wolters EC, et al. Frontal–striatal abnormalities underlying behaviours in the compulsive–impulsive spectrum. *J Neurol Sci.* (2010) 289:55–9. doi: 10.1016/j.jns.2009.08.043
11. Hutton SB. Cognitive control of saccadic eye movements. *Brain Cogn*. (2008) 68:327–40. doi: 10.1016/j.bandc.2008.08.021
12. Jaafari N, Rigalleau F, Rachid F, Delamillieure P, Millet B, Olié JP, et al. A critical review of the contribution of eye movement recordings to the

neuropsychology of obsessive compulsive disorder. *Acta Psychiatr Scand*. (2011) 124:87–101. doi: 10.1111/j.1600-0447.2011.01721.x
13. Theleritis C, Evdokimidis I, Smyrnis N. Variability in the decision process leading to saccades: a specific marker for schizophrenia? *Psychophysiology* (2014) 51:327–36. doi: 10.1111/psyp.12178
14. Agam Y, Greenberg JL, Isom M, Falkenstein MJ, Jenike E, Wilhelm S, et al. Aberrant error processing in relation to symptom severity in obsessive–compulsive disorder: a multimodal neuroimaging study. *Neuroimage Clin*. (2014) 5:141–51. doi: 10.1016/j.nicl.2014.06.002
15. Damilou A, Apostolakis S, Thrapsanioti E, Theleritis C, Smyrnis N. Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. *Psychophysiology* (2016) 53:796–805. doi: 10.1111/psyp.12630
16. Kloft L, Kischkel E, Kathmann N, Reuter B. Evidence for a deficit in volitional action generation in patients with obsessive-compulsive disorder. *Psychophysiology* (2011) 48:755–761. doi: 10.1111/j.1469-8986.2010.01138.x
17. Lennertz L, Rampacher F, Vogeley A, Schulze-Rauschenbach S, Pukrop R, Ruhrmann S, et al. Antisaccade performance in patients with obsessive–compulsive disorder and unaffected relatives: further evidence for impaired response inhibition as a candidate endophenotype. *Eur. Arch. Psychiatry Clin Neurosci*. (2012) 262:625–34. doi: 10.1007/s00406-012-0311-1
18. Maruff P, Purcell R, Tyler P, Pantelis C, Currie J. Abnormalities of internally generated saccades in obsessive–compulsive disorder. *Psychol Med*. (1999) 29:1377–85. doi: 10.1017/S0033291799008843
19. McDowell JE, Clementz BA. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. *Exp Brain Res* (1997) 115:333–44. doi: 10.1007/PL00005702
20. Rosenberg DR, Dick EL, O'Hearn KM, Sweeney JA. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. *J Psychiatry Neurosci*. (1997) 22:29–38.
21. Spengler D, Trillenberg P, Sprenger A, Nagel M, Kordon A, Junghanns K, et al. Evidence from increased anticipation of predictive saccades for a dysfunction of fronto-striatal circuits in obsessive–compulsive disorder. *Psychiatry Res*. (2006) 143:77–88. doi: 10.1016/j.psychres.2005.08.020
22. Tien AY, Pearlson GD, Machlin SR, Bylsma FW, Hoehn-Saric R. Oculomotor performance in obsessive-compulsive disorder. *Am J Psychiatry* (1992) 149:641–6. doi: 10.1176/ajp.149.5.641
23. van der Wee NJ, Hardeman HH, Ramsey NF, Raemaekers M, van Megen HJ, Denys DA, et al. Saccadic abnormalities in psychotropic-naive obsessive–compulsive disorder without co-morbidity. *Psychol Med*. (2006) 36:1321–6. doi: 10.1017/S0033291706007926
24. Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF. Meta-analysis of the symptom structure of obsessive-compulsive disorder. *Am J Psychiatry* (2008) 165:1532–42. doi: 10.1176/appi.ajp.2008.08020320
25. van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain* (2009) 132:853–68. doi: 10.1093/brain/awn267
26. Figee M, Vink M, de Geus F, Vulink N, Veltman DJ, Westenberg H, et al. Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biol Psychiatry* (2011) 69:867–74. doi: 10.1016/j.biopsych.2010.12.003
27. Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML. Distinct neural correlates of washing, checking, and hoarding symptomdimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry* (2004) 61:564–76. doi: 10.1001/archpsyc.61.6.564
28. Leopold R, Backenstrass M. Neuropsychological differences between obsessive-compulsive washers and checkers: a systematic review and meta-analysis. *J Anxiety Disord*. (2015) 30:48–58. doi: 10.1016/j.janxdis.2014.12.016
29. Coe BC, Munoz DP. Mechanisms of saccade suppression revealed in the anti-saccade task. *Phil Trans R Soc B* (2017) 372:20160192. doi: 10.1098/rstb.2016.0192
30. Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cogn Sci*. (2012) 16:43–51. doi: 10.1016/j.tics.2011.11.003
31. Piras F, Piras F, Chiapponi C, Girardi P, Caltagirone C, Spalletta G. Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex* (2015) 62:89–108. doi: 10.1016/j.cortex.2013.01.016
32. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* (2003) 160:636–45. doi: 10.1176/appi.ajp.160.4.636
33. Riesel A, Endrass T, Kaufmann C, Kathmann N. Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: evidence from unaffected first-degree relatives. *Am J Psychiatry* (2011) 168:317–24. doi: 10.1176/appi.ajp.2010.10030416
34. Cavedini P, Zorzi C, Piccinni M, Cavallini MC, Bellodi L. Executive dysfunctions in obsessive-compulsive patients and unaffected relatives: searching for a new intermediate phenotype. *Biol Psychiatry* (2010) 67:1178–84. doi: 10.1016/j.biopsych.2010.02.012
35. Chamberlain SR, Fineberg NA, Menzies LA, Blackwell AD, Bullmore ET, Robbins TW, et al. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *Am J Psychiatry* (2007) 164:335–8. doi: 10.1176/ajp.2007.164.2.335
36. Rajender G, Bhatia MS, Kanwal K, Malhotra S, Singh TB, Chaudhary D. Study of neurocognitive endophenotypes in drug-naïve obsessive–compulsive disorder patients, their first-degree relatives and healthy controls. *Acta Psychiatr Scand*. (2011) 124:152–61. doi: 10.1111/j.1600-0447.2011.01733.x
37. Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, Del Campo N, et al. Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain* (2007) 130:3223–36. doi: 10.1093/brain/awm205
38. First MB, Spitzer RL, Gibbon M, Williams JB. (1997). *User's Guide for the Structured Clinical Interview for DSM-IV axis I Disorders SCID-I: Clinician Version*. Arlington: American Psychiatric Association Publishing.
39. Wittchen HU, Zaudig M, Fydrich T. (1997). *Skid. Strukturiertes Klinisches Interview für DSM-IV. Achse I und II. Handanweisung*. Göttingen: Hogrefe.
40. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, et al. The yale brown obsessive compulsive scale: II. *Validity Arch Gen Psychiatry* (1989) 46:1012–6. doi: 10.1001/archpsyc.1989.01810110054008
41. Hand I, Büttner-Westphal H. Die yale-brown obsessive compulsive scale (Y-BOCS): Ein halbstrukturiertes Interview zur Beurteilung des Schweregrades von Denk-und Handlungszwängen. *Verhaltenstherapie* (1991) 1:223–5.
42. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, et al. The obsessive-compulsive inventory: development and validation of a short version. *Psychol Assess*. (2002) 14:485–96. doi: 10.1037/1040-3590.14.4.485
43. Gönner S, Leonhart R, Ecker W. The obsessive–compulsive inventory-revised (OCI-R): validation of the German version in a sample of patients with OCD, anxiety disorders, and depressive disorders. *J Anxiety Disord*. (2008) 22:734–749. doi: 10.1016/j.janxdis.2007.07.007
44. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* (1979) 134:382–9. doi: 10.1192/bjp.134.4.382
45. Neumann NU, Schulte RM. *Montgomery and Asberg Depression Rating Scale. Deutsche Fassung*. Erlangen: Perimed Fachbuch Verlagsgesellschaft (1989).
46. Hautzinger M, Keller F, Kühner C. *Beck Depressions-Inventar (BDI-II)*. Frankfurt: Harcourt Test Services (2006).
47. Steer RA, Ball R, Ranieri WF, Beck AT. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychol Rep*. (1997) 80:443–6. doi: 10.2466/pr0.1997.80.2.443
48. Laux L, Spielberger CD. *Das State-Trait-Angstinventar: STAI*. Göttingen: Beltz Test (2001).
49. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Psychologists Press (1970).
50. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry* (1993) 50:975–90. doi: 10.1001/archpsyc.1993.01820240059008
51. Richter J, Eisemann M, Richter G. German version of the temperament and character inventory. *Zeitschrift für Klinische Psychologie-Forschung und Praxis* (2000) 29:117–126.

52. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci*. (2004) 5:218–28. doi: 10.1038/nrn1345
53. Bey K, Kloft L, Lennertz L, Grützmann R, Heinzel S, Kaufmann C, et al. Volitional saccade performance in a large sample of patients with obsessive-compulsive disorder and unaffected first-degree relatives. *Psychophysiology* (2017) 54:1284–1294. doi: 10.1111/psyp.12884
54. Bey K, Meyhöfer I, Lennertz L, Grützmann R, Heinzel S, Kaufmann C, et al. Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder. *Eur Arch Psychiatry Clin Neurosci*. (2018) doi: 10.1007/s00406-018-0899-x. [Epub ahead of print].
55. Smyrnis N. Metric issues in the study of eye movements in psychiatry. *Brain Cogn*. (2008) 68:341–58. doi: 10.1016/j.bandc.2008.08.022
56. Ettinger U, Meyhöfer I, Mehta MA, Kumari V, Corr PJ, Williams SC, et al. Effects of lorazepam on saccadic eye movements: the role of sex, task characteristics and baseline traits. *J Psychopharmacol*. (2018) 32:678–690. doi: 10.1177/0269881118772450
57. Wöstmann NM, Aichert DS, Costa A, Rubia K, Möller HJ, Ettinger U. Reliability and plasticity of response inhibition and interference control. *Brain Cogn*. (2013) 81:82–94. doi: 10.1016/j.bandc.2012.09.010
58. Klein C, Heinks T, Andresen B, Berg P, Moritz S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biol Psychiatry* (2000) 47:978–90. doi: 10.1016/S0006-3223(00)00234-1
59. Baer L. Factor analysis of symptom subtypes of obsessive compulsive disorder and their relation to personality and tic disorders. *J Clin Psychiatry* (1994) 55 :18–23.
60. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med*. (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
61. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. (2012) 49:1–15. doi: 10.18637/jss.v049.i05
62. Ray JW, Shadish WR. How interchangeable are different estimators of effect size? *J Consult Cli. Psychol*. (1996) 64:1316–25. doi: 10.1037/0022-006X.64.6.1316
63. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. Orlando: Academic Press (1985).
64. Abramovitch A, Abramowitz JS, Mittelman A. The neuropsychology of adult obsessive–compulsive disorder: a meta-analysis. *Clin Psychol Rev*. (2013) 33:1163–71. doi: 10.1016/j.cpr.2013.09.004
65. Shin NY, Lee TY, Kim E, and Kwon JS. Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. *Psychol Med*. (2014) 44:1121–30. doi: 10.1017/S0033291713001803
66. Walitza S, Wendland JR, Gruenblatt E, Warnke A, Sontag TA, Tucha O, et al. Genetics of early-onset obsessive–compulsive disorder. *Eur Child Adolesc Psychiatry* (2010) 19:227–35. doi: 10.1007/s00787-010-0087-7
67. Hasler G, Pinto A, Greenberg BD, Samuels J, Fyer AJ, Pauls D, et al. Familiality of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD Collaborative Genetics Study. *Biol Psychiatry* (2007) 61:617–25. doi: 10.1016/j.biopsych.2006.05.040
68. Munoz DP, Wurtz RH. Role of the rostral superior colliculus in active visual fixation and execution of express saccades. *J Neurophysiol* (1992) 67:1000–2. doi: 10.1152/jn.1992.67.4.1000
69. Hou JM, Zhao M, Zhang W, Song LH, Wu WJ, Wang J, et al. Resting-state functional connectivity abnormalities in patients with obsessive–compulsive disorder and their healthy first-degree relatives. *J Psychiatry Neurosci*. (2014) 39:304–11. doi: 10.1503/jpn.130220
70. West R, Murphy KJ, Armilio ML, Craik FI, Stuss DT. Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain Cogn*. (2002) 49:402–19. doi: 10.1006/brcg.2001.1507
71. Fassbender C, Scangos K, Lesh TA, Carter CS. RT distributional analysis of cognitive-control-related brain activity in first-episode schizophrenia. *Cogn Affect Behav Neurosci*. (2014) 14:175–88. doi: 10.3758/s13415-014-0252-4
72. Weissman DH, Roberts KC, Visscher KM, Woldorff MG. The neural bases of momentary lapses in attention. *Nat Neurosci*. (2006) 9:971–78. doi: 10.1038/nn1727
73. Murtha S, Cismaru R, Waechter R, Chertkow H. Increased variability accompanies frontal lobe damage in dementia. *J Int Neuropsychol Soc*. (2002) 8:360–72. doi: 10.1017/S1355617702813170
74. Hatzimanolis A, Bhatnagar P, Moes A, Wang R, Roussos P, Bitsios P, et al. Common genetic variation and schizophrenia polygenic risk influence neurocognitive performance in young adulthood. *Am J Med Genet B Neuropsychiatr Genet*. (2015). 168:392–401. doi: 10.1002/ajmg.b.32323
75. Costas J, Carrera N, Alonso P, Gurriarán X, Segalàs C, Real E, et al. Exon-focused genome-wide association study of obsessive-compulsive disorder and shared polygenic risk with schizophrenia. *Transl Psychiatry* (2016) 6:e768. doi: 10.1038/tp.2016.34
76. Glahn DC, Knowles EE, McKay DR, Sprooten E, Raventós H, Blangero J, et al. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. *Am J Med Genet B Neuropsychiatr Genet*. (2014) 165:122–30. doi: 10.1002/ajmg.b.32221
77. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn Sci*. (2012) 16:81–91. doi: 10.1016/j.tics.2011.11.009
78. Nicolini H, Arnold P, Nestadt G, Lanzagorta N, Kennedy JL. Overview of genetics and obsessive–compulsive disorder. *Psychiatry Res*. (2009) 170:7–14. doi: 10.1016/j.psychres.2008.10.011
79. Van Grootheest DS, Bartels M, Van Beijsterveldt CE, Cath DC, Beekman AT, Hudziak JJ, et al. Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12,14, and 16. *J. Am. Acad. Child Adolesc. Psychiatry* (2008) 47:1182–8. doi: 10.1097/CHI.0b013e3181825abd
80. *International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS)*. Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Mol Psychiatry* (2017) 23:1181–8. doi: 10.1038/mp.2017.154
81. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. *Mol Psychiatry* (2015) 20:337–44. doi: 10.1038/mp.2014.43
82. Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, et al. Genome-wide association study of obsessive-compulsive disorder. *Mol Psychiatry* (2013) 18:788–98. doi: 10.1038/mp.2012.85
83. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch Gen Psychiatry* (2007) 64:1242–50. doi: 10.1001/archpsyc.64.11.1242
84. Malone SM, Iacono WG. Error rate on the antisaccade task: heritability and developmental change in performance among preadolescent and late-adolescent female twin youth. *Psychophysiology* (2002) 39:664–73. doi: 10.1111/1469-8986.3950664
85. Vaidyanathan U, Malone SM, Donnelly JM, Hammer MA, Miller MB, McGue M, et al. Heritability and molecular genetic basis of antisaccade eye tracking error rate: A genome-wide association study. *Psychophysiology* (2014) 51:1272–84. doi: 10.1111/psyp.12347
86. Ettinger U, Kumari V, Crawford TJ, Davis RE, Sharma T, Corr PJ. Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology* (2003) 40:620–8. doi: 10.1111/1469-8986.00063
87. Browne HA, Gair SL, Scharf, JM, Grice, DE. Genetics of obsessive-compulsive disorder and related disorders. *Psychiatr Clin North Am*. (2014) 37:319–335. doi: 10.1016/j.psc.2014.06.002
88. Davis LK, Yu D, Keenan CL, Gamazon ER, Konkashbaev AI, Derks EM, et al. Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture. *PLoS Genet.* (2013) 9:e1003864. doi: 10.1371/journal.pgen.1003864

89. Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Børglum AD, Breen G, et al. Psychiatric genomics: an update and an agenda. *Am J Psychiatry*. (2017) 175:15–27. doi: 10.1176/appi.ajp.2017.17030283
90. Bey K, Lennertz L, Riesel A, Klawohn J, Kaufmann C, Heinzel S, et al. Harm avoidance and childhood adversities in patients with obsessive–compulsive disorder and their unaffected first-degree relatives. *Acta Psychiatr Scand*. (2017) 135:328–38. doi: 10.1111/acps.12707
91. Ettelt S, Grabe HJ, Ruhrmann S, Buhtz F, Hochrein A, Kraft S, et al. Harm avoidance in subjects with obsessive-compulsive disorder and their families. *J Affect Disord*. (2008) 107:265–9. doi: 10.1016/j.jad.2007.08.017
92. Shin DJ, Jung WH, He Y, Wang J, Shim G, Byun MS, et al. The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder. *Biol Psychiatry* (2014) 75:606–14. doi: 10.1016/j.biopsych.2013.09.002
93. Green JF, King DJ, Trimble KM. Antisaccade and smooth pursuit eye movements in healthy subjects receiving sertraline and lorazepam. *J Psychopharmacol*. (2000) 14:30–6. doi: 10.1177/026988110001400103

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