Aus dem Zentrum für Neurologie und Psychiatrie der Universität zu Köln
Klinik und Poliklinik für Psychiatrie und Psychotherapie
Direktor: Universitätsprofessor Dr. med. F. Jessen

Deep brain stimulation and sensorimotor gating in tourette syndrome and obsessive-compulsive disorder

Tiefe Hirnstimulation und sensomotorisches Gating bei Tourette Syndrom und Zwangsstörung

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Sophia Katharina Schleyken
aus Moers

promoviert am 08. November 2023

Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität zu Köln
2024

Dekan: Universitätsprofessor Dr. med. G. R. Fink

1. Gutachter: Professor Dr. med. J. Kuhn
2. Gutachter: Universitätsprofessor Dr. med. M. Barbe

Erklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertationsschrift ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskriptes habe ich Unterstützungsleistungen von folgenden Personen erhalten:

Herrn Professor Dr. Jens Kuhn
Frau Dr. Sina Kohl

Weitere Personen waren an der Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe einer Promotionsberaterin/eines Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertationsschrift stehen.

Die Dissertationsschrift wurde von mir bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Die dieser Dissertationsschrift zugrundeliegende Studie wurde von mir zum wesentlichen Teil selbst entworfen und konzipiert. Darüber hinaus halfen Frau Dr. Sina Kohl und Herr Prof. Dr. Jens Kuhn beim Studienkonzept. Ich habe den vollständigen Datensatz ohne Unterstützung erhoben. Die Datenauswertung mit der Software für statistische Datenanalyse „SPSS“ erfolgte zum wesentlichen Teil durch mich selbst mit Unterstützung durch Frau Dr. Sina Kohl, Herrn Prof. Dr. Jens Kuhn und Herrn Dr. Jeremy Franklin. Die aus dieser Studie entstandene Publikation wurde im ersten Entwurf vollständig allein durch mich erstellt. Die Schrift wurde anschließend mit Unterstützung durch Frau Dr. Sina Kohl, Herrn Prof. Dr. Jens Kuhn, Herrn Dr. Juan Carlos Baldermann, Herrn Dr. Daniel Huys, Herrn Dr. Jeremy Franklin und Frau Prof. Dr. Veerle Visser-Vandewalle bearbeitet. Weitere Personen waren an der Erstellung der vorliegenden Publikation nicht beteiligt. Zusammenfassend erkläre ich hiermit, dass ich den wesentlichen Teil der Arbeit an der Studie geleistet habe.

Erklärung zur guten wissenschaftlichen Praxis:

Ich erkläre hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten (Amtliche Mitteilung der Universität zu Köln AM 132/2020) der Universität zu Köln gelesen habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Köln, den 08.04.2023

Unterschrift: .....

Danksagung

An dieser Stelle möchte ich allen beteiligten Personen meinen großen Dank aussprechen, die mich bei der Anfertigung meiner Dissertation unterstützt haben.

Mein besonderer Dank gilt Herrn Prof. Dr. Jens Kuhn und Dr. Sina Kohl für die hervorragende Betreuung und große Unterstützung bei der Umsetzung dieser Arbeit. Auch über die Dissertation hinaus habt Ihr mich für das Fach Psychiatrie begeistert und mir mit großem Engagement bei meiner Dissertation sowie auch bei meiner beruflichen Laufbahn zur Seite gestanden.

Außerdem möchte ich mich bei den Co-Autoren des dieser Arbeit zugrundeliegenden Papers Dr. Juan Carlos Baldermann, Dr. Daniel Huys, Dr. Jeremy Franklin und Prof. Dr. Veerle Visser-Vandewalle für die produktiven Gespräche und Anregungen bedanken.

Meinen Eltern Sylvia und Martin, meinem Bruder Jonas und meinem zukünftigen Ehemann Nico danke ich für die emotionale Unterstützung. Ihr seid meine Basis, welche es mir überhaupt erst ermöglichte, mich mit meinem Dissertationsthema auseinanderzusetzen.

Table of contents

List of abbreviations

ACC	anterior cingulate cortex
CBT	cognitive behavioural therapy
CM-Pf	centromedian-parafascicular nucleus
CSTC	cortico-striato-thalamo-cortical
DBS	deep brain stimulation
EMG	electromyography
GABA	gamma-aminobutyric acid
HC	healthy control
NAc	nucleus accumbens
OCD	obsessive-compulsive disorder
PA	pulse alone
PET	positron emission tomography
PnC	caudal pontine reticular nucleus
PP	prepulse
PPI	prepulse inhibition
PPTg	pedunculopontine tegmental nucleus
SG	sensorimotor gating
SSRI	selective serotonin reuptake inhibitor
STN	subthalamic nucleus
TS	tourette syndrome
vALIC	ventral anterior limb of the internal capsule
YBOCS	Yale-Brown Obsessive Compulsive Scale
YGTSS	Yale Global Tic-Severity Scale

1. Zusammenfassung

Das Gehirn eines Individuums wird mit einer Flut von Stimuli konfrontiert, welche durch das ‚Sensomotorische Gating' (SG) gefiltert werden, um eine Fokussierung auf relevante Stimuli zu ermöglichen. Eine valide Nachweismethode des SG stellt die sogenannte Präpulsinhibition (PPI) des Schreckreflexes dar [1]. Hierbei wird die Verringerung des Schreckreflexes durch ein vorheriges sensorisches Warnsignal gemessen und kann in Prozent angegeben werden. Der Mechanismus des SG und der PPI wird mit Hirnstrukturen in Verbindung gebracht, die partiell in die sogenannten kortiko-striato-thalamo-kortikalen Bahnen eingebunden sind. Diese wiederum gelten bei verschiedenen psychiatrischen Erkrankungen wie z.B. dem Tourette-Syndrom (TS) und bei Zwangserkrankungen (OCD) als dysreguliert [1]. Dementsprechend war die Fragestellung naheliegend zu untersuchen, ob bei Patienten mit dem TS und OCD Veränderungen des SG zu detektieren sind und ob diese durch eine neuromodulative Behandlung mittels tiefer Hirnstimulation (THS) beeinflusst werden [1]. Die Studie, welche dieser Dissertation zugrunde liegt, untersuchte die PPI des akustischen Schreckreflexes von 10 Patienten mit TS und 8 Patienten mit OCD, welche mit THS der Thalamus-Kerne beziehungsweise der ‚striatalen Region' vorderer Schenkel der Capsula interna und des angrenzenden Nucleus accumbens behandelt wurden sowie 18 gesunden Kontrollen, welche in Alter und Geschlecht mit den Patienten übereinstimmten [1]. Die PPI der THS-Kohorten wurde zweimalig (in der Stimulation-ON sowie Stimulation-OFF Bedingung) unter randomisierten Bedingungen gemessen [1]. Die statistische Analyse ergab keine signifikanten Unterschiede der PPI (gemessen in Prozent) zwischen der ON- und OFF-Bedingung der Patienten mit TS sowie auch der Patienten mit OCD. Wir fanden jedoch eine signifikant verringerte PPI bei Patienten mit dem TS in der ON-Bedingung im Vergleich zu gesunden Kontrollen. Allerdings ergab sich kein signifikantes Ergebnis hierfür in der OFF-Bedingung [1]. Die Studie weist Limitationen auf. Die Stichprobengrößen sind aufgrund der Seltenheit des Therapieverfahrens bei psychischen Erkrankungen klein. Um die Gruppengröße nicht noch weiter zu verkleinern, stellte der Konsum psychoaktiver Medikation und Nikotin kein Ausschlusskriterium dar, obwohl bekannt ist, dass beide Faktoren die Präpulsinhibition beeinflussen. Die Tiefe Hirnstimulation umfasst einen initialen neurochirurgischen Eingriff, jedoch wurde vor der Operation kein Ausgangswert der PPI erhoben. Dies verhindert die Möglichkeit, Auswirkungen der chronischen Stimulation im Längsschnittverlauf zu untersuchen[1]. Unter Berücksichtigung der Limitationen konnte durch die Studie zusammenfassend gezeigt werden, dass die PPI bei Patienten mit TS beeinträchtigt ist. Dieses Ergebnis stimmt mit bisherigen Studien überein. Frühere Forschungsergebnisse unserer Arbeitsgruppe, die auch eine beeinträchtigte PPI bei Patienten mit OCD gezeigt hatten, konnten nicht repliziert werden. Die Beeinträchtigung des SG spielt bei vielen psychiatrischen Erkrankungen eine zentrale Rolle, sodass weitere wissenschaftliche Studien erfolgen sollten, um die zugrundeliegenden krankheitsspezifischen

neuroanatomischen und funktionalen Verschaltungen zu entwirren, sowie Einflussmöglichkeiten durch neuromodulative Verfahren zu verifizieren[1].

2. Summary

The environment surrounding an individual causes a flood of stimuli, which are filtered in the brain with a mechanism called sensorimotor gating (SG), to ensure that only relevant information reaches consciousness. An important mechanism in this process is the startle reflex. Prepulse inhibition is a scientific tool to measure the reduction of the startle reflex that is induced by a prior sensory warning signal and can be stated in percent. The mechanism of SG and PPI are discussed to cross brain pathways in functional loops starting in the cortex, passing on to the striatum, to the thalamus and returning to the cortex (CSTC-loops). Researchers suggests that in Tourette-Syndrome (TS) and Obsessive-Compulsive-Disorder (OCD), these pathways are dysregulated [1]. Thus, the question arose if abnormal SG can be detected in patients with TS and OCD and how the neuromodulative treatment with deep brain stimulation (DBS) influences SG [1]. The study underlying this dissertation investigated changes of PPI of the acoustic startle reflex by DBS of the thalamic nuclei and the anterior limb of the internal capsule nucleus accumbens respectively, and included 10 patients with TS, 8 patients with OCD and 18 healthy controls, who matched in age and gender [1]. Patients were measured twice, during active stimulation (ON-condition) and when the stimulation was switched off (OFF-condition), and randomization of the order of condition was used to enhance reliability [1]. We found no significant difference in PPI (measured in percent) between the ON- and OFF-condition in patients with TS as well as patients with OCD. Yet, the analysis revealed significantly reduced PPI levels of patients with TS in the ON-condition compared to healthy controls. However, the comparison did not reach significance for the OFF-condition [1]. As DBS is still a rare treatment in psychiatric diseases, a small sample size limits our results. Furthermore, nicotine and psychoactive medication have been shown to influence PPI levels but were not controlled for in our study. DBS includes an operative neurosurgical procedure, but we did not collect PPI data before the surgical procedure took place so that we were not able to assess any data of long-term stimulation effect [1]. Keeping these limitations in mind, the main finding of our study was that PPI is altered in patients with TS which is supported by research results to date. However, our results differ from our previously published data where we found significantly reduced PPI levels in patients with OCD. As the exact effect of deep brain stimulation on cortical functions remains unknown, we suggest further research to disentangle its potentials and limitations [1].

3. Introduction

3.1 The startle reflex and mechanism of prepulse inhibition

Imagine working focused on your laptop. You were alone in your office when you started working, but suddenly you realize your colleague is sitting at his desk next to yours. You would probably say “Oh hi, I didn’t hear you come in!”, though this is only partly correct. Because beside environmental stimuli that you are aware of, your organism is confronted with a flood of stimuli that remain unaware. In this case, you heard your colleague come in – your brain just decided that the information was not relevant so that it did not reach consciousness. Therefore, the organism suppresses (“gates”) irrelevant sensory, cognitive and motor signals to ensure that only important information reaches consciousness. This mechanism is called **sensorimotor gating (SG)**. This inhibitory control of afferent and efferent signals affects automatic, involuntary processes, as well as behaviour and cognition [2].

An experimental measure of SG is **Prepulse inhibition** (PPI), which involves the startle reflex – an evolutionary essential reaction of protection. A confrontation of a human being with an unexpected auditory, tactile or visual stimulus results in a reflexive contraction of skeletal and facial muscles [1]. This reflex occurs in all mammals and primates [2]. The auricular startle reflex involves the exposure to a loud noise. The acoustic stimulus is forwarded within the cochlear brain nerve and reaches the cochlear nuclei within the brainstem. If the original stimulus intensity reaches a certain threshold of about 80dB for humans, the information passes on to the ventrolateral tegmental nucleus and the caudal pontine reticular nucleus (PnC) within the brainstem. The PnC excites the motor neurons, followed by the motor response [2]. Among other muscle contractions, a blink reflex occurs. The amount of this startle reflex can be modulated. The protection of processing hypothesis suggests that if a sensory signal (which will be called pulse in this experimental measure) is preceded by a weaker sensory signal (called prepulse in this experimental measure) within an interval of 30-500ms, sensory processing is buffered by inhibiting the pulse processing [1]. Therefore, the cochlear nuclei not only project to relevant structures of the startle reflex. They also send excitatory signals to the inferior colliculus and the pedunculopontine tegmental nucleus (PPTg) within the brainstem. The PPTg is a central pattern within the mechanism of SG. It inhibits the PnC which in turn leads to an inhibition of the motor response. Therefore, it receives multiple afferences.

Whereas the direct connection from the cochlear nuclei and an indirect loop connection over the inferior and superior colliculus activate the PPTg, it is also modulated by limbic and basal ganglia structures: the medial prefrontal cortex / orbitofrontal cortex, basolateral amygdala and nucleus accumbens (NAc) display inhibitory effects on the nuclei [1]. Lesions within these limbic

and basal ganglia tissues as well as lesions of the superior and inferior colliculus and even more the PPTg have been shown to induce changes of PPI [2]. In consequence, research focuses on changes of PPI in mental diseases associated with dysfunctions within the CSTC and limbic loops. It is most thoroughly investigated in patients with schizophrenia, a psychiatric disorder that is associated with hyperactive dopaminergic abnormalities in the basal ganglia [3]. Nowadays, abnormal levels of inhibition have been found in a range of other neuropsychiatric disorders associated with (partially dopaminergic) alterations in the above-mentioned loops, including the TS and OCD [2,4,5].

As stated earlier, PPI can be measured using the blink reflex as a part of the startle reaction [1]. The blink reflex occurs as a contraction of the orbicularis ocular muscle. The amount of muscle contraction can be measured using electromyography (EMG). The amplitude of muscle contraction in micro-Volt is recorded within a given interval after every prepulse, pulse or prepulse-and-pulse stimulus (16). As the amplitude of muscle contraction is individual, the amount of inhibition of startle by the prepulse-to-pulse trials compared to pulse alone trials can be stated in percent for the purpose of comparability.

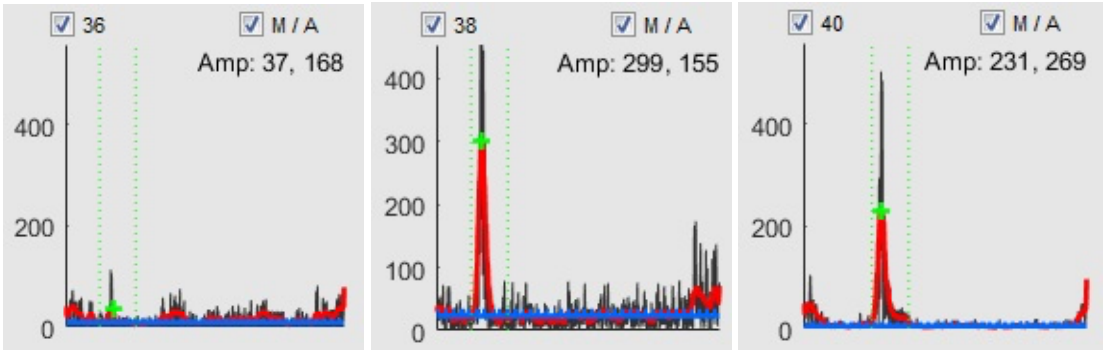


Figure 1. Example of an EMG signal following prepulse alone (PPA) stimulus, pulse alone (PA) stimulus and a stimulus with prepulse to pulse stimulus-onset asynchrony (SOA) of 120ms. Description of trials is given from left to right. No major muscle contraction of the orbicular oculi muscle occurs following PPA stimulus. Muscle contraction occurs following PA stimulus and following the stimulus with SOA of 120ms. A reduced amplitude can be observed in the SOA 120 trial compared to the PA trial in terms of prepulse inhibition (PPI). Source: custom written Matlab program (MathWorks, Natick, MA, USA) developed in our clinic to visually inspect and analyse PPI data [1].

3.2 Tourette Syndrome

3.2.1. Diagnostic criteria and pathophysiology

TS is characterized by multiple motor tics and at least one vocal tic, which can occur independent from each other [1]. To **diagnose** TS in a psychiatric patient, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), symptoms need to occur before the age of 18 and need to persist for at least one year, though they may wax

and wane [6]. Comorbid psychiatric conditions include attention deficit disorder, OCD, anxiety disorders and depression [6,7]. Short, rapid and non-rhythmic muscle contractions cause both stereotypic motor tics and – in case they involve contractions of respiratory, laryngeal, oral or nasal muscles – vocal tics [1]. This may involve either isolated muscles (especially of the face and neck) or a variety of muscle groups, thereby causing simple or coordinated complex tics. Tics usually surface as normal motor gestures, although they characteristically occur involuntary. Patients describe uncomfortable sensory phenomena such as bodily sensations or an irresistible urge to move, both of which occur prior to a motor or vocal tic. This phenomenon called the premonitory urge. They often interpret the subsequent tic as a rather intentional movement to relieve the involuntary sensation. In reaction to this, many patients can temporarily suppress or postpone tics. The appearance of tics is also modulated by the mental state. Relaxation, distraction or acts with need for selective attention decrease tic frequency, whereas stress increases its frequency [8]. Tic spectrum and severity are commonly assessed by the Yale Global Tic-Severity Scale (YGTSS). This semi-structured interview allows a disease-experienced interviewer to evaluate the number, complexity, intensity, frequency and interference of a patient's symptoms [9]. Though in about 90% of patients tics do not persist or at least improve in adulthood [10], the remaining 10% of patients tend to show a chronic, sometimes even progressive and pharmacotherapeutic-resistant course of disease.

The origin and **pathophysiology** of the premonitory urge and the following tics are still under investigation. Especially the frontal and prefrontal areas, the ventral striatum, corpus callosum, thalamus and midbrain seem to interfere with the regulation of movement sequences. There is a scientific consensus that the connectivity between these areas is altered, but the exact mechanisms of dysfunction remain a matter of debate and further research. Neuroimaging studies in accordance with research of sensorimotor integration suggest that tics may originate from dysfunctions within the CSTC loops, causing thalamo-cortical overactivity [8]. On a biochemical basis, abnormalities in a wide range of neurotransmitters have been described. Noradrenergic, glutamatergic, opioid, cholinergic, gamma-aminobutyric acid (GABAergic) and serotoninergic transmitter systems may therefore all affect the pathology of TS in a certain extent [11]. However, pathophysiological models predominantly focus on a hypothesized disinhibition of CSTS loops caused by deficient transmissions of dopamine. Various nuclear imaging studies, cerebrospinal fluid analyses and post-mortem brain studies report on hyperfunctions or an imbalance within the dopamine system [11]. Specifically, studies showed that the number of cortical and striatal dopamine transporters increased and that binding to the basal ganglia and release of dopamine is altered [12].

3.2.2. Treatment

In many patients, tics barely limit psychosocial functioning and therefore medical treatment is not required. Nevertheless, in other cases the tic symptomatology may cause individual distress factors such as uncertainty about the condition or self-stigma [13]. To address the entire psychosocial and motoric symptom spectrum, educational therapy is implemented. By improving the knowledge of illness and treatment options in a patient, this therapeutic approach aims to enhance coping strategies and motivate autonomous handling. Habit reversal training (HRT) rather focuses on symptom reduction by developing an awareness of when tics are about to occur. In reaction to the urge to tic, the patient can develop behaviour focussed on stopping the tic or redirecting it to socially accepted gestures. Yates et al. compared these **psychotherapeutic approaches** and found that both treatments decreased tic severity and the patient's overall quality of life. Habit reversal training was found to be more effective in reducing motor tics, measured by the YBOCS [14]. A meta-analysis in 2014 indicated that empirically, habit reversal training is the treatment of choice [15].

The European Clinical Guidelines for Tourette Syndrome and Other Tic Disorders suggest that **pharmacological treatment** should be considered if tics cause subjective discomfort, functional interference or social problems [16]. In accordance with research results of the underlying pathophysiology of TS, up to now the modulation of the dopaminergic transmission is the most effective pharmacological treatment approach [12,17]. Typical antipsychotics preferably antagonize dopaminergic D2 receptors so that thalamo-cortical movement-related activity is inhibited. High potency agents such as haloperidol, pimozide and fluphenazine are effective for both motor and vocal tic reduction in about 70% of patients [12,14,17]. The high frequency of adverse effects, especially regarding the extrapyramidal symptoms and drowsiness, limits the use of typical antipsychotics. Atypical antipsychotics modulate the D2 receptor in a smaller extent and also modulate D3, D4, serotonin- and other receptors. Therefore, the pharmacological agents show smaller extrapyramidal side effects and some of the agents also show a smaller increase of prolactin level compared to typical antipsychotics [17]. Still, reported adverse effects include weight gain, a prolonged cardiac QTc interval, a lowered seizure threshold and drowsiness [12,16-18]. Tetrabenazine and deutetrabenazine inhibit the vesicular monoamine transporter 2. This intracellular particle transports dopamine, norepinephrine and serotonin from the synaptic vesicles to the synapse. Though research data is rather weak, both agents were found to be effective in some rather small studies. Other transmitter systems, such as the noradrenergic, serotoninergic or GABAergic, appear to be involved in the pathophysiology of TS as well. Tic treatment may therefore also involve a range of non-dopaminergic agents. This includes Clonidine and Guanfacine (alpha-2 receptor agonists), baclofen (GABA-B receptor agonist), topiramate (GABA agonist, AMPA receptor

antagonist) and botulinum toxin (neurotoxic acetylcholine release inhibitor) [19]. The efficacy of Valbenazine (the third Vesicular Monoamine Transporter 2 Inhibitor), Cannabinoids, Clonazepam and dopamine D1 receptor antagonists is not sufficiently researched yet but might be further investigated in the future. Notably, psychotherapeutic and pharmacological approaches may not completely eliminate tics. On average, a recent meta-analysis found a median reduction of 53% on the YGTSS by conventional strategies [20]. Still, a significant number of patients do not experience an adequate symptom reduction. In case these symptoms lead to a massive impairment of quality of life, more invasive augmentation strategies such as DBS should be considered (see also Section 3.4).

3.3 Obsessive Compulsive Disorder

3.3.1. Diagnostic criteria and pathophysiology

The obsessive compulsive disorder (OCD) is characterized by recurrent unwanted obsessions, which are defined as urges, thoughts or images that are usually experienced as uncomfortable, and repetitive behaviour or mental acts, called compulsions [21]. The latter either occur as an attempt to neutralize an obsession or to follow certain rules [21]. The content of obsessions and compulsions varies among patients. It frequently includes matters of contamination and purification, persistent doubt, fear of causing harm, thoughts of prohibited or off-limit content, symmetry, religious scrupulosity and superstition. Symptoms are often accompanied by avoidance behaviours. According to the **diagnostic criteria** of DSM-5, symptoms are time-consuming through taking more than one hour per day or cause distress and impairment in important areas of functioning [21]. Furthermore, obsessions and compulsions cannot be affiliated to physiological effects of substances or another physical or mental disorder. The patient characteristically recognizes the absurdity of obsessions and compulsions. Nevertheless, the spectrum of insight ranges from patients that are certain that their obsessive-compulsive contents are true to patients that can define their beliefs as probably not true [22,23]. The age of onset of OCD has a peak in late childhood or early adolescence and again in early adulthood [24]. The severity of symptoms tends to increase during the course of disease and often occurs waxing and waning. Without treatment, a complete illness remission is achieved about 20% of the time. Environmental and genetic factors are hypothesized to have an effect on the development of OCD. Traumatic incidences, infectious pathogens and the post-infectious autoimmune syndrome are associated with a higher risk of developing OCD. Among patients with OCD with an onset in childhood, the risk for first grade relatives to develop OCD is ten times higher. Comorbid psychiatric disorders are common. Anxiety disorders have a high lifetime prevalence of 76%, followed by depressive and bipolar disorders (63%) and tic disorders (30%) [22,23]. Symptoms are commonly assessed with the semi-structured Yale-Brown

Obsessive Compulsive Scale (YBOCS). This clinician-rated, ten-item scale measures the severity of illness with separate sub-scores for the severity of obsessions and compulsions [25].

Hypotheses on the **pathophysiology** of OCD derive from neuropsychological-, neurocircuitry- and neurochemical-based evidence. Neuropsychological studies suggest that the observed higher cognitive impairments in OCD might be induced by dysfunctions within and between frontal patterns and basal ganglia [26-29]. Consistently, neuroimaging data documents alterations within the orbitofrontal cortex, the anterior cingulate cortex (ACC) and patterns within the basal ganglia, particularly the caudate nucleus [30-32]. Considering the overall research conclusions, scientists agree on the hypothesis that obsessive compulsive symptoms occur as a result of hyperactive alterations within the CSTC loops and fronto-striatal connections [32]. On a biochemical basis, abnormalities in the serotoninergic, dopaminergic and glutamatergic system have been described in patients with OCD. However, it is presumed that dysfunctions within the serotoninergic neurotransmission contribute most essentially to the pathophysiology of OCD. Yet, study results regarding the serotonergic neurotransmission are inconclusive as findings varied from increased to similar or decreased binding and availability within regions of interest [33-35].

3.3.2. Treatment

The use of cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs), frequently implemented in combination with each other, is the preferred primary treatment approach. **CBT** involves cognitive reappraisal and behavioural intervention. The latter typically uses exposure-response prevention. The patients are therefore exposed to stimuli provoking obsessions and are then instructed to dissociate themselves from associated compulsions and avoidance behaviours. Among patients who are not able to bear the exposure, clinicians may favour rather cognitive based modalities in CBT treatment [36].

SSRIs exclusively inhibit the reuptake of serotonin into the neuron so that the amount of serotonin in the synaptic clefts increases. This leads to an increased serotoninergic effect on the downstream neuron [37]. Meta-analyses indicate that the SSRI agents Fluvoxamine, Fluoxetine, Paroxetine, Citalopram and Sertraline are all equally effective in the treatment of obsessive- compulsive symptoms. Guidelines recommend the use of SSRIs in the maximal tolerated dose for at least eight to 12 weeks in patients with OCD. Common side effects among SSRIs include gastrointestinal upset (loss of appetite, diarrhea, nausea), agitation, dry mouth, insomnia, headache, jitteriness, vivid dreams and sexual dysfunction [38]. **Tricyclic antidepressants**, including the most commonly used agent clomipramine, inhibit the reuptake of serotonin but also have other modulating effects, such as an interaction with alpha1-adrenergic, muscarinic and histamine receptors [39,40]. Clomipramine remains gold standard for

OCD treatment, though SSRIs are preferred by many clinicians because of their better tolerability. Common side effects of clomipramine include fatigue, blurred vision, tremor, a dry mouth, constipation, hyperhidrosis and an increased risk of arrhythmia as well as seizures at doses greater than 200 milligram (mg) daily [23,41]. In about 25% of patients with OCD, the treatment with an SSRI and/or CBT fails to achieve an adequate symptom reduction [23]. Following the treatment algorithm suggested by several guidelines, clinicians may then consider switching to another SSRI or clomipramine or augment the implemented therapy with additional medication [23,42,43]. **Augmentation** with antipsychotics, either typical or atypical, is effective in about 30% of treatment-refractory patients with OCD. It has been suggested that antipsychotics are more likely to reduce obsessive compulsive symptoms if patients have a co-occuring tic disorder [23]. Emerging evidence furthermore suggests that ketamine, riluzole, N-acetylcysteine, memantine, lamotrigine, celecoxib and ondansetron are effective agents in augmentation strategies [23].

Furthermore, electroconvulsive therapy as well as repetitive transcranial magnetic stimulation are investigated in regard to their effectiveness in patients with OCD [23]. DBS has been accepted as a last resort treatment for patients with OCD that displayed a non-response to conventional treatment [44].

3.4 Deep Brain Stimulation

3.4.1. History and indication

Despite the increasing knowledge on the diagnostic factors, pathophysiology and treatment, a significant percentage of psychiatric patients does not respond adequately to psychological and pharmacological treatment approaches. Such a non-response is generally defined as a symptom reduction of less than 25-35% [23,44]. In consequence, clinicians are in need for further treatment options for patients who are resistant to the conventional strategies. Neurosurgical procedures such as the anterior cingulotomy, capsulotomy, subcaudate tractotomy or limbic leucotomy were invented in the 20th century for treatment-refractory psychiatric patients. Though these techniques have a certain individual response rate in some disorders [23], the invasiveness limits its use. DBS is a stereotactic procedure that is considered safe in comparison, due to its lesser invasiveness and the increasing amount of data describing the efficacy and adverse effects. DBS was initially invented to treat neurologic movement disorders but is nowadays also accepted as a last resort treatment for OCD. Furthermore, its efficacy is being investigated for a variety of psychiatric disorders including treatment resistant patients with TS, addiction, mood disorders, anxiety disorders, anorexia, autism, schizophrenia and dementia [1]. Across diseases, inclusion criteria to a clinical DBS trial include the presence of a chronic and severe psychiatric disease that highly impairs daily functioning. An insufficient response to conventional therapies must be recorded in the patient's treatment history. In

Cologne, patients with OCD were only operated if at least one trial of CBT, two treatment trials with an SSRI over at least ten weeks at maximum dosage, one trial with clomipramine over ten weeks at maximum dosage and an augmentation approach with antipsychotic medication, lithium or buspirone failed to achieve an adequate symptom reduction [45]. Patients with TS needed to undergo at least two approaches with antidopaminergic neuroleptics in adequate dosage for at least three months [46]. In several cases additional approaches with benzodiazepines and alpha agonists had been ineffective. An estimated 500 psychiatric patients have been operated in the world so far [44].

3.4.2. Implantation and mechanism of action

Multipolar electrodes are implanted in a specific brain area associated with the pathophysiology of the disorder. Detailed information about the surgical procedure itself is found in publications of randomised controlled trials such as in Ackermans et al. 2011 [47] and Baldermann et al. 2021 [48]. By a pulse generator implanted in the chest thereafter, electric impulses are chronically delivered to the patient's brain. The stimulation settings are optimized in the following months, for example it is possible to regulate the pulse width and frequency. Typical stimulation parameters are square biphasic waveforms, a frequency of 120 hertz (Hz), a pulse width of 60 to 210 microseconds (µs) and amplitudes of two to five volt (V) [49]. Yet, the exact impact of the impulses on the brain networks is not fully understood and seems to vary by indication and stimulation allocation. Initially it has been suggested that electric impulses inhibit excessive pathological activity in the stimulated area analogous to the effect of local lesions caused by the described neurosurgical procedures. Recently, it has been shown that DBS much rather restores brain activity and connectivity not only in the stimulated area but also in distant areas with projections to the stimulated area. McIntyre et al. therefore pointed out the importance of understanding the effect that DBS has on the axonal transportation of information to other cells rather than just the effect on the targeted soma [50]. Therefore all information that contributes to the understanding of the complex networks is important.

3.4.3. Neurophysiology of the CSTC loops

Closely interconnected with an immeasurable amount of functional neuron networks, the CSTC loops enable cognition, movement and behaviour. Its nomenclature follows the flow of information within a network of structurally spread but functionally connected grey matter tissues.

Whereas the primary motor cortex, the premotor cortex and the prefrontal associative cortex are involved in the planning and execution of movement, grey matter apart from the cortex called the **basal ganglia** controls the initiation, the amount, direction, force and speed of movement. They are functionally connected to each other, the thalamus and the cortex through the basal ganglia main- and side-loops. The main entrance of the basal ganglia with excitatory

afferences of the cortex is the striatum, which consists of the NAc, the caudate nucleus and the putamen. To a great extent, the nucleus accumbens forms the ventral striatum. In animal models, it has been shown that the nucleus accumbens' outer shell can be considered as a part of the extended amygdala, whereas the core in particular is part of the basal ganglia associated with motor functions related to reward and reinforcement [51-53].

The transmitter dopamine plays an important role in the enforcement of movement. It activates one part of the striatum and inhibits another part of the striatum. With its mostly inhibitory efferences the striatum modulates the pallidum through the indirect and direct pathway: a) it inhibits the medial pallidum, which then cannot inhibit the thalamus and therefore enforces movement or b) it inhibits the lateral pallidum, which in term cannot inhibit the STN and finally leads to an inhibition of movement. The striatum also directly inhibits the substantia nigra. Its pars compacta, which aims to give feedback to the striatum, therefore cannot activate the movement enforcing part of the striatum and cannot inhibit the movement inhibitory part of the striatum. In consequence movement is inhibited. At the same time, its pars reticularis cannot inhibit the thalamus and therefore movement is enforced. The STN excites the medial pallidum and the substantia nigra pars reticularis and thus inhibits movement. The ventral thalamic nuclei excite the motor cortex [51-57]. This chain of inhibitory and excitatory modulation forms one main- and two different side-loops in order to create feedback to the motor cortex and enable precise movement sequences. Figure 1 presents relevant structures involved in these loops.

The excitation and inhibition within the main- and side-loops of the basal ganglia eventually lead to either an inhibition or missing inhibition of the ventral thalamic nuclei. The **thalamus** filters and interconnects information. The filtered neuronal impulses are then forwarded to their destination within the brain, allowing for the information to reach consciousness [51,58]. The group of ventral thalamic nuclei receive the above-mentioned afferences from the basal ganglia. Other afferences originate from the cerebellum and from the premotor and motor cortex. The nuclei integrate the information and then project to the premotor (anterior ventral nuclei), motor (lateral ventral nuclei) and sensory cortex (posterior ventral nuclei), thereby aiming to coordinate voluntary motor functions and to process and filter sensory information. Beside the ventral 'motor and sensory' part, the anterior thalamic nuclei are seen as the 'emotional' part of the thalamus, whereas the medial thalamic nuclei project to the prefrontal cortex [51,58].

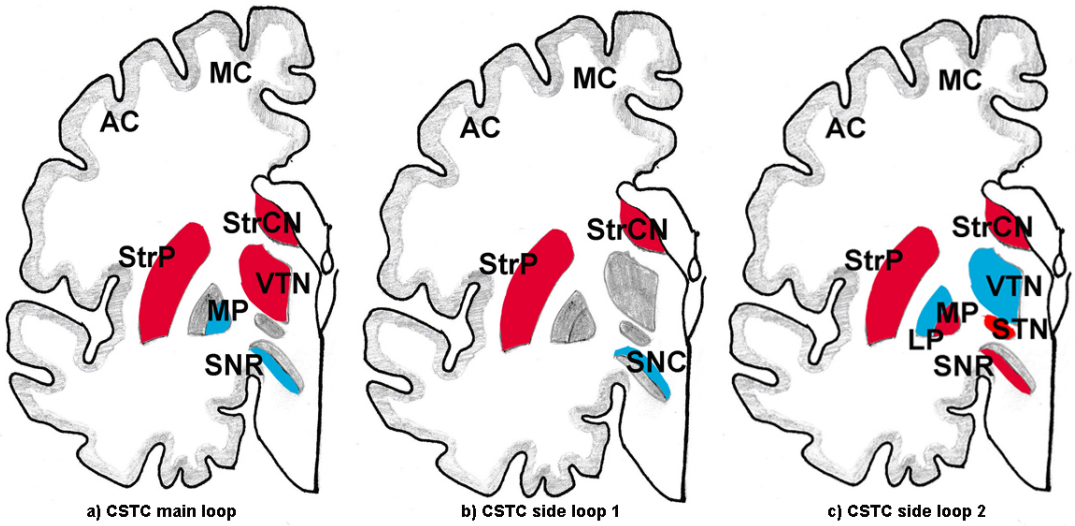


Figure 2. Structures involved in the Cortico-striato-thalamo-cortical (CSTC) main- and sideloops. Excited tissues are highlighted in red, inhibited tissues in blue. a) movement drive in the associative cortex (excites)→ striatum (inhibits)→ medial pallidum and substantia nigra pars reticularis (disinhibits)→ ventral thalamic nuclei (excite)→ motor cortex. b) movement drive in associative cortex (excites)→ striatum (inhibits)→ substantia nigra, pars compacta (cannot excite the movement enforcing part, neither inhibit the movement inhibitory part of the striatum) c) movement drive in associative cortex (excites)→ striatum (inhibits) → lateral pallidum (disinhibits)→ subthalamic nucleus (excites)→ medial pallidum and substantia nigra pars reticularis (inhibit)→ ventral thalamic nuclei (inhibit)→ motor cortex. AC, associative cortex; MC, motor cortex; StrP, pallidum of the striatum; StrCN, caudate nucleus of the striatum; LP, lateral pallidum; MP, medial pallidum; SNR, substantia nigra pars reticuaris; SNC, substantia nigra pars compacta; STN, subthalamic nucleus; VTN, ventral thalamic nuclei. Source: own illustration based on the internet anatomy atlas of the university of cologne [59].

3.4.4. The putative effect of DBS on the CSTC loops

In OCD, the most common DBS targets include the ventral anterior limb of the internal capsule (vALIC), the NAc, the STN and the inferior thalamic peduncle. It is hypothesized that DBS induces a down-regulation of excessive neural activation in cortico-striatal and fronto-striatal loops, with the connections of the medial part of the prefrontal cortex (mPFC) and the ACC to the striatum being of particular interest in this matter [60-62]. On a biochemical basis, one study found increased serotonin levels in the frontal areas and increased dopamine levels in the striatum following DBS of the NAc [63]. Figee et al. supposed, that dopamine is secondarily increased to compensate for serotonergic deficits in OCD and found that following DBS of the NAc or successful treatment with a serotonin reuptake inhibitor (SRI), dopamine levels of their patients increased in the striatum [64].

Just as in patients with OCD, the knowledge of how DBS neurophysiologically effects patients with TS is still incomplete. Investigated targets include the centromedian thalamic region, the anteromedial or posteroventrolateral medial pallidum and the anterior limb of the internal capsule [44]. The centromedian thalamic nucleus / parafascicular complex (CM-Pf) and the

medial pallidum are most commonly targeted. Research results indicate a modulation of dopaminergic transmission by the treatment with DBS of the thalamus [65,66].

3.4.5. The clinical effect of DBS on the CSTC loops

Analogous to pharmacological response cut-off values, clinical response of patients with OCD to DBS is commonly defined as a symptom decrease of at least 30-35% on the YBOCS. Alonso et al. estimated in their meta-analysis that the response rate of OCD to DBS is 60%. They reported on a mean reduction of 45,1%. The targets neither differed in the percentage of responders nor in the mean YBOCS reduction [67]. The overall quality of life has been found to approach a degree of 90% [44]. Clinically, DBS for OCD can have immediate positive effects on mood and anxiety. However, obsessive and compulsive symptoms are characteristically observed to decrease over weeks and months [68]. Other positive effects include improvements in depression, addicted behaviour and weight loss. In contrast, other studies reported on a temporary elevation of anxiety and panic symptoms as well as a transient state of hypomania, especially when the stimulation was switched off again [44].

In patients with TS, the YGTSS is a common scale to assess the response to DBS. Recently, an international multicentre registry reported on a mean symptom improvement of 45% on the mean YGTSS. The publication included data from 185 patients, stimulated in the four most common targets mentioned above [69]. The meta-analysis of Baldermann et al. found that in 81% of patients, symptoms were reduced by at least 25% [66]. Clinical DBS trials reported on positive effects on anxiety [70]. However, adverse events are common and most frequently include transient dysarthria, paresthesias and weight gain [69].

3.5 Research Question

CSTC loop dysregulations are assumed to be involved in the pathophysiology of TS and OCD, therefore its substrates are targeted by DBS. On the other hand, its substrates are also assumed to be involved in the process of SG, which is related to the amount of central inhibitory functioning of an individual. Which effect does the overlap of these assumptions have? It is hypothesized, that central inhibitory functioning is deficient in patients with TS and OCD. Furthermore, it is hypothesized that DBS of the CSTC substrates modulates brain activity and connectivity relevant for the central inhibitory functioning [1].

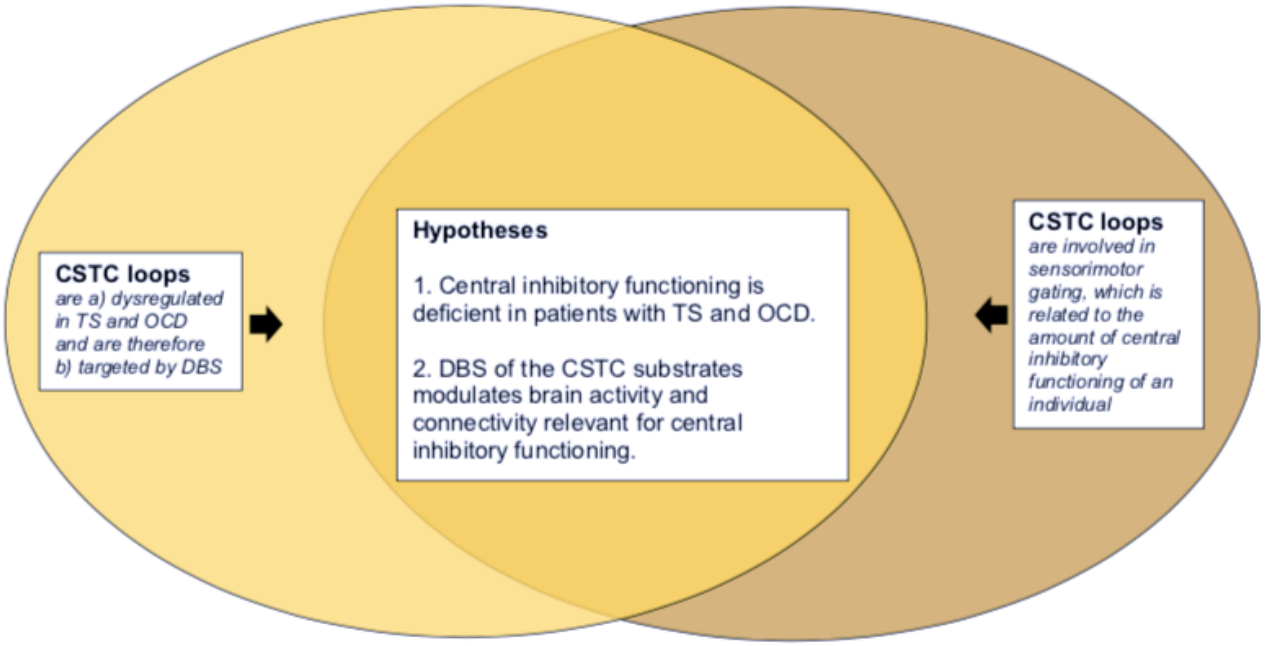


Figure 3. Hypotheses. Visualization of the thought process of how the hypotheses were built. CSTC loops, cortico-striato-thalamo-cortical loops; TS, tourette syndrome; OCD, obsessive-compulsive disorder; DBS, deep brain stimulation. Source: own illustration.

4. Publication

Deep brain stimulation and sensorimotor gating in tourette syndrome and obsessive-compulsive disorder

Authors: Sophia Schleyken (1), Juan Baldermann (1), Daniel Huys (1), Jeremy Franklin (2), Veerle Visser-Vandewalle (3), Jens Kuhn (1,4), Sina Kohl (1)

(1) Department of Psychiatry and Psychotherapy, University Hospital of Cologne, Kerpener Strasse 62, 50937, Cologne, Germany
(2) Institute of Medical Statistics and Computational Biology, University of Cologne, Kerpener Strasse 62, 50937, Cologne, Germany
(3) Department of Stereotactic and Functional Neurosurgery, University of Cologne, Kerpener Strasse 62, 50937, Cologne, Germany
(4) Johanniter Hospital Oberhausen, Department of Psychiatry, Psychotherapy and Psychosomatics, Steinbrinkstrasse 96A, 46145, Oberhausen, Germany

J Psychiatr Res. 2020 Oct:129:272-280.
doi: 10.1016/j.jpsychires.2020.07.016. Epub 2020 Aug 7.

Abstract

Recent translational data suggest that deep brain stimulation (DBS) of the cortico-striato-thalamo-cortical (CSTC) loops improves sensorimotor gating in psychiatric disorders that show deficient prepulse inhibition (PPI), a robust operational measure of sensorimotor gating. To our knowledge we are the first to investigate this effect in patients with Tourette syndrome (TS). We measured PPI of the acoustic startle reflex in patients with TS (N = 10) or Obsessive-Compulsive Disorder (OCD) (N = 8) treated with DBS of the centromedian and ventro-oral internal thalamic nucleus and the anterior limb of internal capsule–nucleus accumbens area respectively, and aged- and gender-matched healthy controls (HC). PPI of the DBS groups was measured in randomized order in the ON and OFF stimulation condition. Statistical analysis revealed no significant difference in PPI (%) of patients with TS between ON (M = 20.5, SD = 14.9) and OFF (M = 25.2, SD = 29.7) condition. There were significantly reduced PPI levels in patients with TS in the ON condition compared to HC (M = 49.2, SD = 10.7), but no significant difference in PPI between TS in the OFF condition and HC. Furthermore, we found no significant stimulation or group effect for OCD and HC (OCD ON: M = 57.0, SD = 8.3; OCD OFF: 67.8, SD = 19.6; HC: M = 63.0, SD = 24.3). Our study has a number of limitations.

Sample sizes are small due to the restricted patient collective. The study was not controlled for use of psychoactive medication or nicotine. Furthermore, we were not able to assess presurgical PPI measurements. In conclusion, we were able to show that PPI is impaired in patients with TS. This finding is in line with recent translational work. With respect to the OCD cohort we were not able to replicate our previously published data. A disability in sensorimotor gating plays a pivotal role in many psychiatric disorders therefore more research should be conducted to disentangle the potential and limitations of modulating sensorimotor gating via brain stimulation techniques.

Introduction

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor tics and at least one vocal tic (American Psychiatric Association, 2000). Brief, rapid and non-rhythmic muscle contractions cause tic movements and – if involving contractions of respiratory, laryngeal, oral or nasal muscles – vocal sounds (Berardelli et al., 2003). Obsessive-Compulsive Disorder (OCD) is characterized by recurrent, intrusive thoughts or images and repetitive, ritualistic and time-consuming behaviours (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). Both disorders share pathophysiological hypotheses of dysfunctions within the cortico-striato-thalamo-cortical (CSTC) loops (McIntyre and Hahn, 2010; Saxena et al., 1998). Highly disabling psychosocial consequences are frequently observed in both disorders, including teasing and isolation (Cox et al., 2019; Murray and Lopez, 1996). Though the course of TS and OCD can be effectively influenced by an adequate treatment, a significant number of patients neither profit adequately from pharmacological nor from psychological treatment (Ackermans et al., 2013; Denys, 2006). Deep brain stimulation (DBS) is a stereotactic procedure that delivers electric impulses to specific brain targets. Among psychiatric indications, it has been accepted as a last resort treatment for OCD (Alonso et al., 2015) and its efficacy is furthermore investigated in a variety of psychiatric disorders, including treatment-refractory cases of TS (Ackermans et al., 2011; Huys et al., 2016; Kefalopoulou et al., 2015; Maciunas et al., 2007; Welter et al., 2017). Based on the pathophysiological knowledge of the disorders, common DBS targets for OCD and TS are located within the CSTC loops (Kohl et al., 2013). However, the exact impact of the chronic stimulation on the brain networks is not fully understood.

Sensorimotor gating is the suppression of irrelevant information to ensure the ability to focus on relevant stimuli (Swerdlow, 1992). It can be measured using prepulse inhibition (PPI) of the brainstem-mediated startle-reflex. The startle-reflex is assessed by recording the reflexive contraction of skeletal or facial muscles in response to a confrontation with an unexpected and intense stimulus. It is hypothesized that if this stimulus (pulse) is preceded by a weaker

stimulus (prepulse) within an interval of 30–500 ms, an inhibition of pulse processing results in an attenuation of muscle contraction. Forebrain substrates of the CSTC loops, including the medial prefrontal cortex, orbitofrontal cortex, basolateral amygdala and nucleus accumbens regulate the inhibitory tone of PPI (Miller et al., 2010; Saint Marie et al., 2010; Swerdlow et al., 1992; Wan and Swerdlow, 1997).

Tics as well as obsessive-compulsive symptoms are hypothesized to represent deficits in central inhibitory functioning and early filter processing (Swerdlow, 2012; Morein-Zamir, 2010). Thus, deficient PPI shares overlapping psychophysiological as well as neural substrates with OCD and TS. Or as Swerdlow puts it in his review on PPI and TS "it is conceivable that the pathological processes responsible for the loss of PPI in TS patients may also be related to, and even contribute to, the processes responsible for intrusive sensory phenomena in this disorder." (Swerdlow, 2012). Clinical studies underline this relation, there have been several reports on decreased PPI in OCD (Ahmari et al., 2012; de Leeuw et al., 2010; Hoenig et al., 2005; Swerdlow et al., 1993) as well as TS (Castellanos et al., 1996; Swerdlow et al., 2001) (for a review see Kohl et al., 2013 and Swerdlow et al., 2013).

In a preliminary study from 2015, we showed significantly decreased PPI levels in the stimulation OFF-condition in patients with OCD compared to healthy controls (HC) and found a significant difference between ON- and OFF-conditions at the prepulse to pulse stimulus-onset asynchrony (SOA) trials of 200 ms (Kohl et al., 2015). We therefore hypothesize that the stimulation of CSTC substrates modulates brain activity and connectivity relevant for the modulation of PPI and that this effect will be observable in a new cohort of OCD patients as well as in patients with TS. We furthermore hypothesize that PPI is dependent on symptom severity.

Methods

This study has been approved by the Ethics Committee of the Medical Faculty of the University of Cologne and has been carried out in accordance with the latest version of the Declaration of Helsinki, amended in October 2013. All patients underwent DBS surgery as part of clinical trials. Patients with implanted DBS electrodes were recruited from the interdisciplinary outpatient clinic at the University Hospital Cologne. To be included, patients of both disorders had to fulfil diagnostic criteria of OCD or TS, respectively, according to DSM-IV. The course of disease had to be chronic and severe, indicated by a score of 25 or higher on Y-BOCS and a course of disease of over 5 years for patients with OCD, corresponding to highly impaired psychosocial functioning and quality of life. Furthermore, patients were considered treatment refractory, which for OCD was defined by an insufficient response to at least one course of

treatment with cognitive behavioural therapy, at least two trials with selective serotonin reuptake inhibitors, one trial with clomipramine and an augmentation approach with antipsychotic medication, lithium or buspirone. Patients with TS had to show insufficient response to at least three antipsychotic agents of known efficacy in tic disorders and to clonidine. Patients were between 20 and 64 years old and had no other severe medical, neurologic, psychiatric or cogni- tive disorders (Huys and Kohl et al., 2019; Huys et al., 2016). HC were recruited by posters in public facilities and by direct requests to acquaintances of the research team members. HC had to be free of a life- time history of psychiatric and neurologic diseases as well as hearing impairments, assessed by a questionnaire on their medical history. We exclusively tested HC that matched an assigned patient in age (±2 years) and gender. All participants gave their written informed consent after the nature and possible consequences of the study were explained to him/her. Ten patients diagnosed with TS and eight patients diagnosed with OCD, all according to DSM-IV and ICD-10, and 18 HC participated in the study. Patients with TS were stimulated with DBS in the centromedian and ventro-oral internal thalamic nucleus. One patient with TS was stimulated in the internal globus pallidus. Patients with OCD were stimulated with DBS in the nucleus accumbens/anterior limb of the internal capsule (Fig. 1). All patients completed at least six months of active stimulation before their first test session. Then they were tested once during stimulation and once when stimulation was switched off in a pseudo-randomized order. Stimulation parameters were chosen for best clinical results, based on patients' reports. Use of concomitant psychoactive medication at the time of measurement differed between patients. Three patients with TS and seven patients with OCD used antidepressants. Two patients with TS and two patients with OCD used antipsychotics. Two patients with TS did not use any psychoactive medication. Five patients (four with TS, one with OCD) and four HC dropped from further analysis because the individuals were found to be non-startlers according to the human startle eye blink electromyography (EMG) study guidelines (Blumenthal et al., 2005). One HC dropped from further analysis because the individual exhibited a strong startle reflex when he/she was exposed to the prepulse only.

Procedure

The blink reflex, as a component of the auricular startle reflex, and its PPI were measured using EMG of the orbicularis oculi muscle. Surface electrodes were placed lateral to the lateral canthi and inferior to the lower lid in the mid-pupillary line of the right eye. EMG was recorded by a commercially available startle system (SR-HLab, San Diego In- struments, San Diego, CA, USA). The participant was instructed to relax and look out of the window during the test session. Stimuli were applied over headphones. The background noise was 70 dB(A) sound pressure level (SPL) broadband white noise. Acoustic stimuli consisted of bursts of 20 ms

white noise with uncontrolled instant rise time. Startle eliciting stimuli were presented at 110 dB(A) SPL, and prepulse stimuli were presented at 80 dB(A) SPL. The test session consisted of an acclimation period of 5 min, followed by three blocks with a total of 60 trials. The first and third block were identical and consisted of five pulse-alone (PA) trials. The second block was composed of 50 trials, ten of which were PA trials, ten were prepulse alone (PPA) trials and 30 were prepulse + pulse (PP) trials. The PP trials consisted of three groups differing in their SOA. The paradigm included ten trials each with an SOA of 60 ms (PPI60), 120 ms (PPI120) and 200 ms (PPI200). All different trial types in the second block were intermixed and presented in a pseudo-randomized order. EMG was measured for 250 ms after every stimulus. Yale- Brown Obsessive-Compulsive Scale (Y-BOCS) for OCD and Yale Global Tic Severity Scale (YGTSS) for TS were conducted prior to DBS surgery and at 12 months follow up.

Data acquisition and processing

EMG data was analysed using a custom written Matlab program (MathWorks, Natick, MA, USA) developed in our clinic to visually inspect and analyse PPI data. As previously explained in our study of Kohl et al., (2015), we applied a high-pass filter at 28 Hz, a low-pass filter at 300 Hz using fourth-order Butterworth Filter, a 50 Hz notch filter and a hampel filter with a filter window of ten Hz between one and 290 Hz with a threshold of five. Due to short epochs, the outlier detector was not applied to the complex spectrum but to the signal amplitude, taking into account a potential phase shift. The EMG signal was subsequently rectified and smoothed with a moving average at a time constant of ten.

We visually inspected all data and excluded any trial featuring excessive noise in the EMG signal and any trials with an amplitude maximum that was out of the measured timeframe or if a spontaneous blink occurred immediately before or after the stimulus onset. Percentages of excluded trials were all beneath 50%. Criteria for qualifying the EMG signal as an actual startle response were defined in accordance with guidelines for human startle eye blink EMG studies (Blumenthal et al., 2005). The latency window was set for 130 ms after pulse onset and minimum response amplitude was set at two standard deviations above baseline, which was defined by the PPA trials, measured at the end of each trial for 80 ms. The highest amplitude in a given time window was identified as the response peak. PPI (%) was calculated using the following formula: [(mean PA – mean PP)/mean PA] x 100. PPI values were calculated for the three SOA types separately. After- wards the mean of all SOA trials was calculated and used for further analyses. The data were inspected by two independent raters.

Statistical analysis

We calculated the mean startle magnitude for both rater data sets by averaging the response magnitude of all included trials. Interrater variability was assessed by the calculation of an intraclass correlation coefficient (ICC). ICC was >90% for all data, so that we applied the mean of the two data sets for further calculations. Owing to small sample sizes, normal distribution of outcome variables could not be confirmed, so we applied non-parametric tests. For within-subject comparisons (ON versus OFF condition) we used the paired Wilcoxon signed-rank test. Group differences between patients and matched HC were analysed with the Mann-Whitney *U* test. Pearson correlation coefficients of PPI data with symptom score reduction on Y-BOCS/YGTSS and duration of stimulation were calculated.

Previously, our study team published PPI data on 8 patients with OCD in an identical study design (Kohl et al., 2015). We pooled this previous data with our present data and repeated analyses to check for consistency of our results in this extended data set.

For this exploratory study, statistical tests were not adjusted for multiple testing. Calculations were done using Excel (Microsoft, Red- mond, WA, USA) and SPSS (IBM, Armonk, NY, USA).

Results

Six patients diagnosed with TS, seven patients diagnosed with OCD and 13 HC were included in the statistical analysis. On average, patients diagnosed with TS (M = 26.3 years, SD = 4.2) were younger than patients diagnosed with OCD (M = 48.4, SD = 10.6). The percentage of females was lower in patients diagnosed with TS (1 female/5 male) than in patients diagnosed with OCD (4 female/3 male). Patient groups did not differ significantly from their HC groups with respect to mean age and gender distribution. For detailed sociodemographic and clinical information please see Table 1.

Within-subject comparison

Within the group of patients with TS the Wilcoxon signed-rank test revealed no significant difference between PPI values in the ON (M = 20.5, SD = 14.9) and OFF (M = 25.2, SD = 29.7) stimulation conditions; $Z=-0.524, p=0.60$.

Likewise, within the group of OCD patients, the Wilcoxon signed-rank test revealed no significant difference between PPI values in the ON (M = 57.0 SD = 8.3) and OFF (M = 67.8, SD = 19.6) stimulation conditions; $Z = -1.521$, $p = 0.128$.

Between-subject comparison

We performed Mann-Whitney U tests for between-subject analyses, two for the TS and two for the OCD subgroups to compare their mean PPI values in ON- and OFF-conditions with HC. The test revealed a significant difference between patients with TS in ON-condition (M = 20.5, SD = 14.9) compared to HC (M = 49.2, SD = 10.7, U = 1.00, p = 0.006). Results in OFF-condition (M = 25.2, SD = 29.7, U = 7.00, p = 0.078) compared to HC were not significant (Fig. 2).

There was no significant difference in the Mann-Whitney *U* test for patients with OCD in ON-condition (U = 14.00, p = 0.180) as well as OFF-condition (U = 23.00, p = 0.848) compared to HC (M = 63.0, SD = 24.3).

In a second step, we pooled our current data with the PPI data of Kohl et al., (2015) (8 patients with OCD and 8 age- and gender-matched HC) and repeated the analysis with a total of 15 patients with OCD and 15 HC. Methodological procedure was the same in both studies. There was a significant difference in the Mann-Whitney *U* test between patients with OCD in ON-condition (M = 56.5, SD = 13.0) compared to HC (M = 67.4, SD = 18.9, U = 59.00, p = 0.026). Results in OFF-condition (M = 56.9, SD = 18.9, U = 75.00, p = 0.126) compared to HC were not significant (Fig. 3).

We tested our PPI data for correlation with symptom severity scores, measured by YGTSS or Y-BOCS. There was a very weak negative and non-significant correlation of PPI and symptom severity score reduction from baseline to 12 months follow up in our TS cohort measured by YGTSS (M = 66.7, SD = 32.0) in the ON-condition (r = − 0.11; p = 0.833) and OFF condition (r = − 0.03; p = 0.95). In our OCD cohort, there was a positive, but non-significant correlation of PPI and symptom severity score reduction from baseline to 12 months follow up measured by Y-BOCS (M = 27.1, SD = 14.3) in the ON-condition (r = 0.54; p = 0.212) and OFF-condition (r = 0.09; p = 0.855). When the OCD cohort of Kohl et al., (2015) was included in the analysis, there was a significant positive correlation (M = 22.3, SD = 30.4, r = 0.72; p = 0.003) between PPI in ON-condition and the Y-BOCS score reduction after 12 months of stimulation (OFF-condition r = 0.15; p = 0.602). Thus, higher symptom score reduction on treatment with DBS was associated with higher levels of PPI.

Furthermore, we tested our PPI data for correlation with duration of stimulation, measured by the time since surgery in months. There was a negative and non-significant correlation of PPI and duration of stimu- lation in our OCD cohort (time since surgery M = 53.0 months, SD = 24.3, ON-condition r = − 0.64; p = 0.119, OFF-condition r = − 0.73; p = 0.065), but no relevant

correlation for TS (time since surgery M = 36.7 months, SD = 16.0, ON-condition r = − 0.15; p = 0.780, OFF-condition r = − 0.08, p = 0.884) as well as the extended OCD cohort with data of Kohl et al., (2015) (time since surgery M = 81.0 months, SD = 70.2, ON-condition r = − 0.15; p = 0.957, OFF-condition r = − 0.27; p = 0.329).

Discussion

We were not able to find differences in PPI between ON- and OFF- conditions of DBS, neither in TS nor in OCD. We found markedly lower PPI levels in patients with TS compared to HC, the difference being significant for the ON condition only. PPI levels in OFF condition were comparably low to the ON condition, however they did not reach significance when compared to HC due to higher standard deviation. This is congruent with our hypothesis of deficient central inhibitory functioning in patients with TS and prior studies investigating PPI in non-DBS TS samples (Castellanos et al., 1996; Swerdlow et al., 2001). Failure to detect significant differences may be due to the small sample sizes and consequent lack of statistical power. We used Wilcoxon tests because the small sample size does not allow reliable assessment of the normality of the distribution. However, we additionally conducted paired t-tests as they have more power. These results were also not significant. Larger patient samples might be able to detect an effect of stimulation. Possible causes of different PPI levels of HC and boys with TS have been investigated by Buse and colleagues, who showed with functional magnetic resonance imaging that significantly reduced PPI of TS patients correlated with reduced blood oxygen level-dependent (BOLD) activity in the middle frontal gyrus, postcentral gyrus, superior parietal cortex, cingulate gyrus, and caudate body. The authors draw the conclusion that reduced recruitment of brain regions responsible for higher-order integration of somatosensory stimuli are responsible for lower PPI levels in young patients with TS (Buse et al., 2016). Similarly, Zebardast et al. found lower BOLD activity during PPI in the medial temporal gyrus, the orbitofrontal cortex, the posterior cingulate cortex and the lateral frontal cortex in adults with TS compared to healthy controls (Zebardast et al., 2013). Taken together, we hypothesize that deficient sensorimotor gating in TS is caused by cortical malfunctioning, while the roles of the thalamic nuclei in psychiatric PPI deficits remain inconclusive.

Against our hypothesis we did not find a difference between HC and OCD patients in our new cohort, irrespectively of the stimulation condition. This finding contradicts the majority of prior PPI research data of patients with OCD. Hoenig et al. Steinman et al. and Ahmari et al. found significantly reduced levels of PPI in patients with OCD (Ahmari et al., 2016; Hoenig et al., 2005; Steinman et al., 2016). Neuroimaging data reveals a range of alterations in patients with OCD with particular relevance to the orbitofrontal cortex and the caudate nucleus of the striatum (Whiteside et al., 2004). Specifically, abnormally high activities in these substrates

have been implicated. However, the observed normal levels of PPI when the stimulation was switched off in our study rather indicate that PPI may not be deficient in patients with OCD who were chronically treated with DBS.

We applied the same methods as in our previous study, where we found a significant difference between HC and OCD patients with the stimulation switched off, as well as a significant effect of stimulation in one condition (Kohl et al., 2015). But of course some differences in the study sample need to be addressed. First, patients of the new cohort received DBS treatment on average for one year before the test sessions took place (M = 53 weeks, SD = 24.34) whereas in the old cohort patients received chronic stimulation for approximately two years (M = 105.5 weeks, SD = 88.8). Whether time since surgery plays a pivotal role and effects of DBS on PPI evolve over a long period of time (two years) is very hypothetical. In our analysis time since surgery was negatively correlated with PPI values, in both stimulation conditions. Second, our cohort of patients with OCD was slightly older than patients from the cohort of Kohl et al., (2015), on average 7.6 years. Though this difference is rather small, an influence on our divergent results cannot be ruled out. The subject's age has been discussed to influence PPI of the acoustic startle. Whereas some studies indicate a maturation of PPI in childhood and a decline of PPI with age (Gebhardt et al., 2012), Ellwanger et al. found that PPI of healthy subjects was rather U-shaped with highest levels in the middle age of on average 41.6 years, compared to declined levels at a young age of on average 29.0 years and an old age of on average 73.2 years (Ellwanger et al., 2003). However, the exact age of the 'PPI peak' cannot be estimated from their analysis. Notably, an increase of PPI to middle age may explain the fact that the HC group of our patients with OCD displayed higher PPI levels than the HC group of our patients with TS as the latter were on average 18.5 years younger. Furthermore, there were less smokers in the current cohort (N = two, 29% of patients) than in the cohort of Kohl et al., (2015) (N = four, 50% of patients). Nicotine has been demonstrated to increase PPI of the acoustic startle in HC (Della Casa et al., 1998; Drobes et al., 2013; Duncan et al., 2001; Kumari et al., 1996). This effect has furthermore been demonstrated in patients with psychiatric disorders including schizophrenia and posttraumatic stress disorder (Kumari et al., 2001; Vrana et al., 2013; Woznica et al., 2009). However, adding the smoking status as a covariate in our analysis showed no significant effect on PPI levels. The two OCD cohorts did not differ in terms of gender, illness duration before surgery, targeted brain area and PPI parameters. Furthermore, in our new OCD cohort, we were not able to find differences in PPI between ON- and OFF-conditions of DBS in OCD, but we found a positive, but non-significant correlation of PPI and symptom severity score reduction from baseline to 12 months follow up measured by Y-BOCS in the ON-condition. And when the OCD cohort of Kohl et al., (2015) was included in the analysis, this positive correlation became significant. Apparently, patients that had greater

improvement of their symptoms also showed a higher PPI score, noteworthy only in the ON-condition. Here again we are missing presurgical PPI data in order to interpret our finding.

To our knowledge we are the first to investigate DBS effects on PPI in humans. Therefore, we need to discuss our results in the context of translational work that has been published. Frequently used rodent models for deficient sensorimotor gating are PPI deficits induced by systemic injection of dopamine receptor agonists or rats selectively bred for high and low levels of PPI. Both have been used in combination with DBS in rats and many studies found significant effects in terms of elevation of PPI by DBS of several brain areas (Posch et al., 2012; Lindemann et al., 2012; Angelov et al., 2014; for an overview see Schwabe and Krauss, 2018). Angelov and colleagues investigated the effect of DBS in Wistar rats selectively bred for low or high PPI levels. Stimulation of the centromedian-parafascicular nucleus of the thalamus significantly enhanced PPI of those animals that were bred for low PPI levels, whereas the stimulation had no effect in high-PPI rats and stimulation of the nucleus accumbens only led to a marginal and non-significant increase of PPI in low and high PPI rats (Angelov et al., 2014). Furthermore, DBS also reduced the neuronal activity of the dorsomedial striatum and the nucleus accumbens, as well as its coherence with the sensorimotor cortex (Elle et al., 2020). Taken together with our present data in patients with OCD and TS these translational observations challenge the pivotal role of the nucleus accumbens in the neuronal circuitry as entry point to modulate PPI. It certainly plays a role in the healthy pathway regulating PPI, as shown by lesion studies (Kodsi and Swerdlow, 1995) and dopaminergic stimulation (Caine et al., 1992). Similar to the thalamic nulcei, the role of the nucleus accumbens in psychiatric PPI deficits remains inconclusive too. Noteworthy, Angelov et al. also found that electrode implantation in the entopeduncular nucleus (EPN; equivalent to the human GPi) already enhanced PPI compared to the measures before surgery and activating the stimulation had no additional effect, indicating that electrode implantation already induced a microlesion effect in the rather small rat EPN (Angelov et al., 2014). Unfortunately, we do not have presurgical and postsurgical data (before active stimulation) to examine the microlesion effect in our sample.

Our negative findings can be interpreted in three different ways. First, due to the very small number of participants we may lack statistical power to find an existing effect of stimulation on sensorimotor gating (type II error). In this case replication of the present study with a larger sample size would bring clarification. Second, there simply might be no effect of DBS on sensorimotor gating. In order to address this hypothesis, a combination of PPI measures with other techniques such as electroencephalography or microelectrode recordings, that could allow the identification of the electrophysiological signatures of different brain sites and recording of neuronal oscillatory activity while PPI could be helpful. Third, DBS might alter

sensorimotor gating but due to long lasting, neuroplastic changes in the brain this effect is not reversed by simply switching of the stimulation device for a day or two. In order to test this possibility, presurgical data would be informative. Unfortunately, we lack this information; future studies should consider these points in order to yield more conclusive data.

Our findings have a number of limitations. Medication did not remain stable during the test sessions although especially dopaminergic and antidopaminergic medication influence PPI in healthy subjects and patients with schizophrenia (Csomor et al., 2008; Quednow et al., 2006; Schellekens et al., 2010; Swerdlow, 2013; Swerdlow et al., 2009; Wynn et al., 2007). In particular, dopamine antagonists were used by 4 of our patients with TS and OCD. Furthermore, 10 out of 13 patients that were included in the initial analysis were using antidepressants. Research findings on the influence of serotoninergic medication on prepulse inhibition are inconclusive (Hammer et al., 2007; Jensen et al., 2007; Phillips et al., 2000; Abel et al., 2007) however an influence on our study results cannot be ruled out. The female hormonal status was not taken into account during our study. Due to the strict operation criteria for DBS, we were only able to measure a small cohort of patients. Exact allocation of electrodes and stimulation parameters varied as they were individually chosen based on best clinical results with particular relevance of one patient with TS being stimulated in the internal pallidal globe. However, this patient did not differ in clinical characteristics from the other patients nor were its PPI values classified as outliers. Furthermore, we were not able to include presurgery PPI measurements to our analysis. This limits the opportunity to examine the effect of chronic stimulation on PPI.

We suggest that results need to be validated through larger sample size in the future, particularly to provide clarity on the mixed results of PPI in OCD. Additionally, to fully understand the effect of DBS on brain mechanisms it may be useful to combine PPI with other recording methods of brain activity such as BOLD-MRI or EEG. Further, presurgical data could add to the understanding of the relationship of DBS and sensorimotor gating.

We conducted the study to contribute to a better understanding of the network effect that DBS of the CSTC loops has on sensorimotor gating of patients with TS and OCD. We did not find any effects, which might be due to lack of statistical power. Looking for future directions, we suggest replicating our study design in a larger patient cohort of TS treated with DBS and control for confounding factors such as sex, hormonal status and medication. In addition, non-invasive brain stimulation in TS and OCD might shed light on cortical modulation of sensorimotor gating networks.

Role of the funding source

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, KFO-219 grant; KU2665/1-2) and the Walter and Marga Boll Foundation. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

CRediT authorship contribution statement

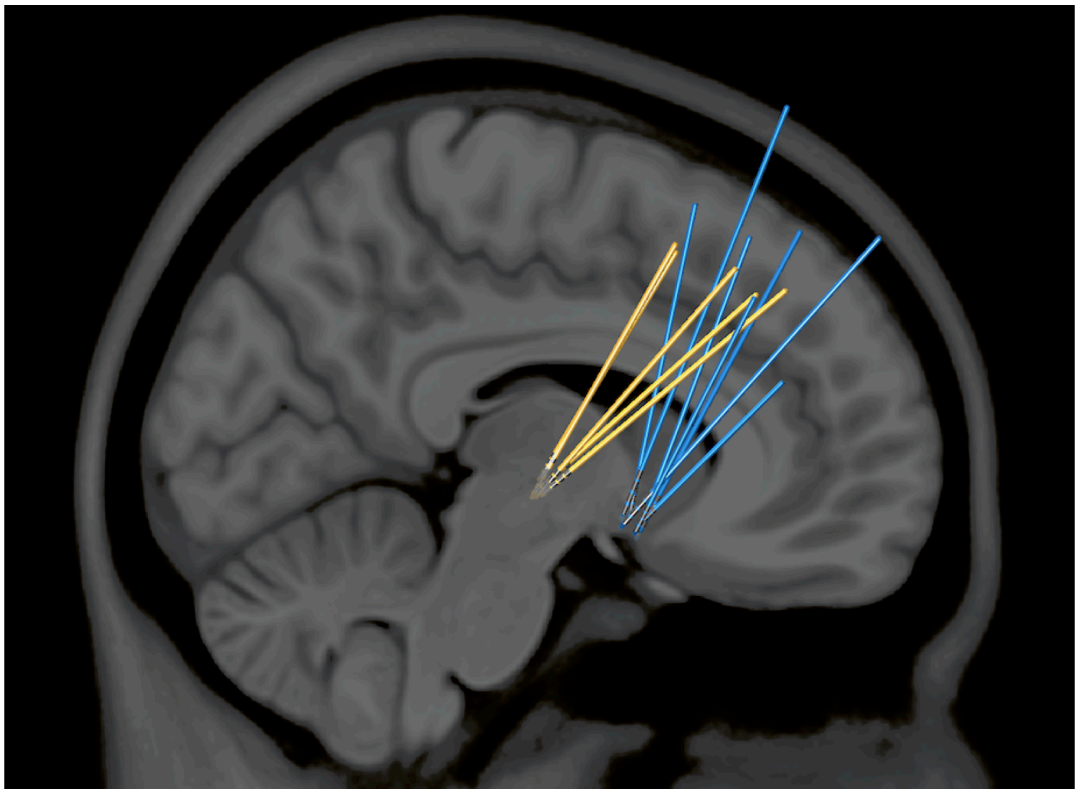
Sophia Schleyken: Investigation, Formal analysis. **Juan Baldermann:** Visualization, Writing - review & editing. **Daniel Huys:** Resources, Writing - review & editing. **Jeremy Franklin:** Formal analysis, Writing - review & editing. **Veerle Visser-Vandewalle:** Resources, Writing - review & editing. **Jens Kuhn:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Sina Kohl:** Conceptualization, Formal analysis, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jens Kuhn has received honoraria from Bayer, Janssen, Lundbeck, Neuraxpharm, Otsuka Pharma, Schwabe and Servier for lecturing at conferences and financial support to travel. He has received financial support for Investigator initiated trials from Medtronic GmbH.

Acknowledgement

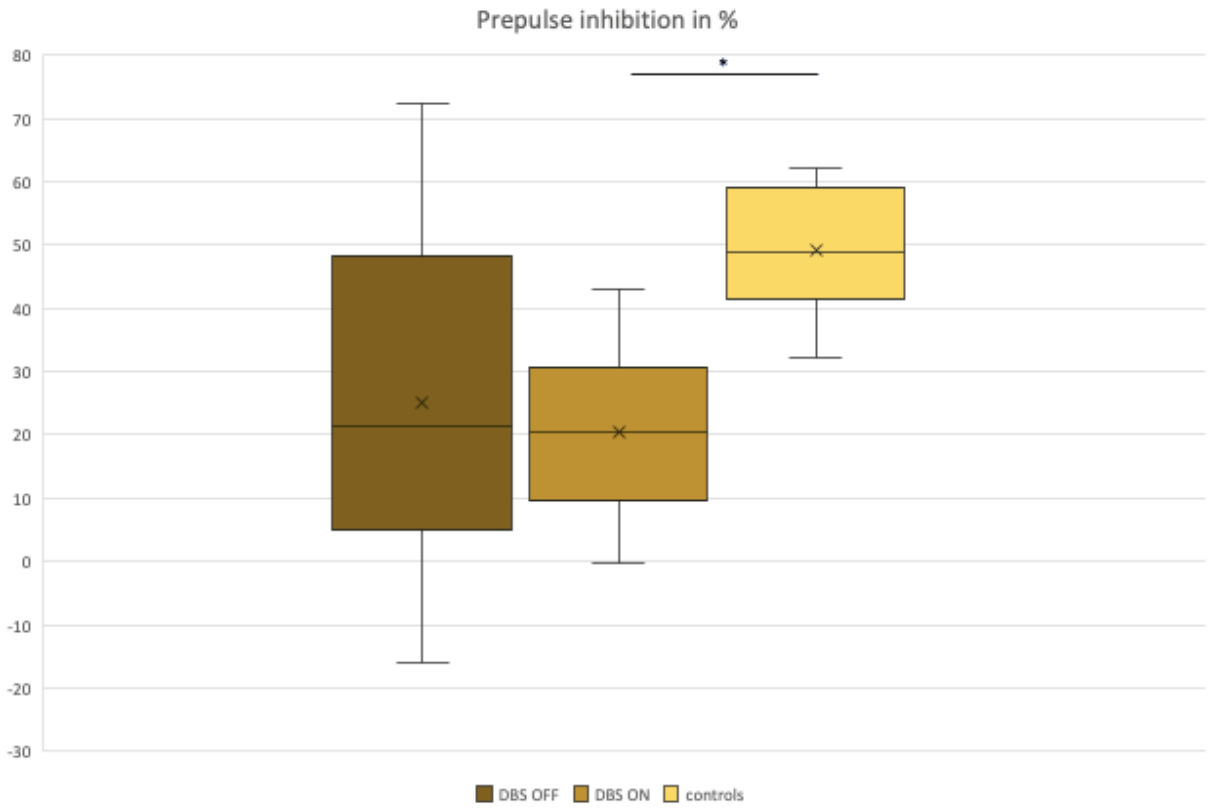
We thank the German Research Foundation (Deutsche Forschungsgemeinschaft, KFO-219 grant; KU2665/1–2) and the Walter and Marga Boll Foundation for financial support. We also thank all participants for taking part in our study.



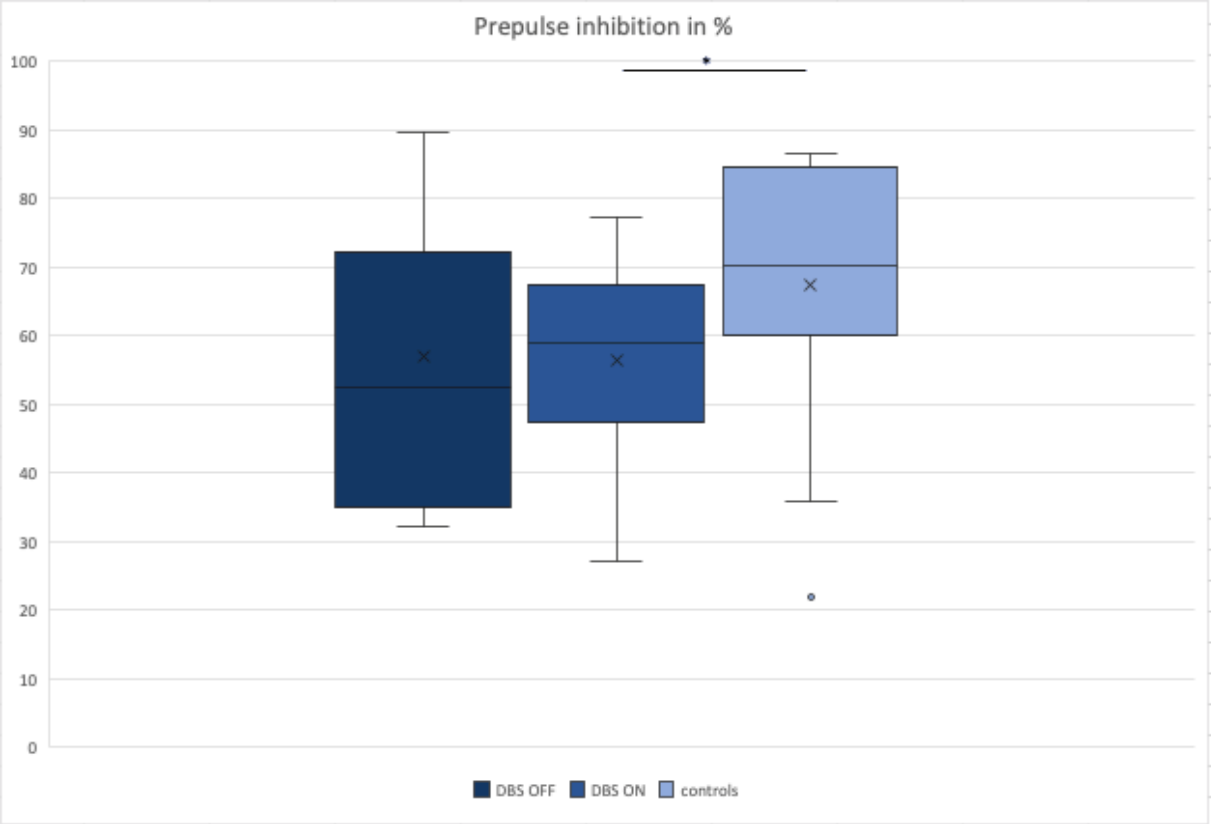
Paper Fig. 1. Localization of right hemispheric deep brain stimulation electrodes in patients with tourette syndrome and patients with obsessive-compulsive disorder in sagittal view. Electrode coordinates were determined using postoperative CT or stereotactic X-ray. All coordinates were transformed into standardized brain space. The figure was generated using the Lead-DBS toolbox (Horn and Kuhn, 2015). In one patient with tourette syndrome, postoperative imaging was not available. Electrodes of patients with tourette syndrome are shown in yellow, electrodes of patients with obsessive- compulsive disorder are shown in blue.

	age (years)	gender	smoking status	comorbidities	Symptom score** at baseline	Symptom score** reduction (%) ***	illness duration before surgery (years)	time since surgery (weeks)	electrode location	Stimulation parameters: Amplitude in V, Frequency in Hz, Pulse width in µs, active poles, time span in off condition (hours) °	Psychotropic medication
TS_01	27	male	yes	none	40	50.0	16	28	CM / VOI	A) 4.1 V, 80 Hz, 120 µs, (1,2, 9, 10); B) 0.5-4.5 V, 40-100 Hz, 120 µs (1,2,9,10) **	no medication
TS_02	33	male	no	OCD	50	100.0	26	35	CM / VOI	5,3 V, 100 Hz, 90-120 µs (2,3,10,11) **	mirtazapine
TS_03	27	male	no	none	30	100.0	19	28	CM / VOI	A) 3.5 V, 130 Hz, 90 µs (2,3,10,11); B) 125 Hz, 90 µs, (3 and 11 with 3.3V, 2 and 10 with 3V) **	no medication
TS_04	25	female	no	OCD, ADHD	50	20.0	23	30	CM / VOI	3.7 V, 90 Hz, 120 µs (2,3,10,11) **	amisulpride, clomipramine, tiaprid
TS_05	20	male	no	none	40	50.0	13	30	CM /VOI	4.8 V, 80 Hz, 150 µs, (1,2,9,10) **	risperidone, aripiprazole, clonazepam, clonidine
TS_06	26	male	yes	none	50	80.0	18	69	GPI	2.5 V, 110 Hz, 60 µs (2,10) **	paroxetine
OCD_01	57	female	yes	none	35	28.6	35	89	Nacc / vALIC	5.2V, 130 Hz, 120 µs (2,3,10,11) **	doxepine, fluoxetine
OCD_02	64	male	no	benzodiazepine addiction	23	30.4	19	82	Nacc / vALIC	4 V, 130 Hz, 150 µs (2,3,10,11) **	sertraline, doxepine, quetiapine, lorazepam
OCD_03	37	female	no	none	33	27.3	27	52	Nacc / vALIC	5V, 130 Hz, 150 µs (2,3,10,11) **	venlafaxine
OCD_04	35	female	no	none	37	8.1	18	51	Nacc / vALIC	5.5 V, 120 Hz, 120 µs (1,2,9,10) **	clomipramine
OCD_05	54	female	no	recurrent depressive episodes	34	14.7	14	25	Nacc / vALIC	6 V, 130 Hz, 90 µs (2,3,10,11) **	fluoxetine
OCD_06	48	male	no	none	28	53.6	20	41	Nacc / vALIC	3.3 V, 130 Hz, 120 µs (2,3,10,11) **	*on:* quetiapine, *off:* quetiapine, clomipramine
OCD_07	44	male	yes	benzodiazepine addiction	37	27.0	37	31	Nacc / vALIC	5.0 V, 130 Hz, 120 µs (1,2,9,10) **	venlafaxine, mirtazapine, alprazolam
OCD_08 *	40	female	no	none	32	6.3	21	144	Nacc / vALIC	1.5 V, 130 Hz, 90 µs, (0,1,2,8,9,10), 17 hours	*on:* fluoxetine, *off:* fluoxetine, aripiprazole
OCD_09 *	45	female	no	none	34	20.6	21	288	Nacc / vALIC	5.5 V, 120 Hz, 150 µs, (2,3,10,11), 3 hours	diazepam, aripiprazole, clomipramine, chlorprothixene
OCD_10 *	36	female	no	eating disorder, social phobia	18	-55.6	27	152	Nacc / vALIC	5.0 V, 130 Hz, 150 µs, (1,3,9,10), 13 hours	duloxetine, quetiapine
OCD_11 *	43	male	yes	none	26	19.2	33	100	Nacc / vALIC	3.8 V, 130 Hz, 90 µs, (2,3,10,11), 10 hours	*on:* citalopram, olanzapine, venlafaxine. *off:* citalopram, olanzapine
OCD_12 *	50	male	yes	none	30	-13.3	34	52	Nacc / vALIC	4.5 V, 130 Hz, 150 µs, (1,2,9,10), 24 hours	*on:* quetiapine, *off:* citalopram, asenapine, quetiapine, zopiclone
OCD_13 *	22	male	yes	none	33	48.5	11	12	Nacc / vALIC	7.0 V, 130 Hz, 120 µs, (2,3,10,11), 10 hours	*on:* medikinet adult, *off:* paroxetine, medikinet adult
OCD_14 *	61	male	no	none	32	75.0	7	48	Nacc / vALIC	6.0 V, 130 Hz, 150 µs, (0,1,8,9), 19 hours	fluoxetine, pregabalin.
OCD_15 *	29	female	yes	recurrent depressive episodes	41	43.9	17	48	Nacc / vALIC	5.5 V, 130 Hz, 120 µs, (0,1,8,9), 10 hours	*on:* sertraline, clomipramine, agomelatine, aripiprazole, *off:* NA

Paper Table 1 Sociodemographic and clinical information of the study population. If not other specified, the information is given for the time at PPI measurement. TS, tourette syndrome, OCD, obsessive-compulsive disorder, ADHD, attention deficit hyperactivity disorder, CM/VOI, centromedian and ventro-oral internal thalamic nucleus, GPI, internal globus pallidus, Nacc/vALIC, nucleus accumbens and anterior limb of the internal capsule. * Kohl et al., (2015), ** Y-BOCS/YGTSS, *** after 12 months of stimulation, ° patients received unipolar stimulation, °° duration in off-condition was 24–72 h.



Paper Fig. 2. Prepulse inhibition in percent in patients with tourette syndrome and controls. Prepulse inhibition was calculated for tourette patient's OFF-session (N = 6), ON-session (N = 6) and healthy controls (N = 6). *Significant difference between groups according to Mann-Whitney *U* test ($p < 0.05$). TS, tourette syndrome.



Paper Fig. 3. Prepulse inhibition in percent in patients with obsessive-compulsive disorder and controls. Prepulse inhibition was calculated for obsessive- compulsive disorder patient's OFF-session (N = 15), ON-session (N = 15) and healthy controls (N = 15). *Significant difference between groups according to Mann-Whitney *U* test ($p < 0.05$). OCD, obsessive-compulsive disorder.

References

Abel, K.M., Allin, M., van Amelsvoort, T., Hemsley, D., Geyer, M.A., 2007. The indirect serotonergic agonist d-fenfluramine and prepulse inhibition in healthy men. Neuropharmacology 52 (4), 1088–1094.
Ackermans, L., Duits, A., van der Linden, C., Tijssen, M., Schruers, K., Temel, Y., Kleijer, M., Nederveen, P., Bruggeman, R., Tromp, S., van Kranen-Mastenbroek, V., Kingma, H., Cath, D., Visser-Vandewalle, V., 2011. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Brain 134 (Pt 3), 832–844.
Ackermans, L., Neuner, I., Temel, Y., Duits, A., Kuhn, J., Visser-Vandewalle, V., 2013. Thalamic deep brain stimulation for Tourette syndrome. Behav. Neurol. 27 (1), 133–138.
Ahmari, S.E., Risbrough, V.B., Geyer, M.A., Simpson, H.B., 2012. Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 37 (5), 1216–1223.
Ahmari, S.E., Risbrough, V.B., Geyer, M.A., Simpson, H.B., 2016. Prepulse inhibition deficits in obsessive-compulsive disorder are more pronounced in females. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 41 (13), 2963–2964.
Alonso, P., Cuadras, D., Gabriels, L., Denys, D., Goodman, W., Greenberg, B.D., Jimenez- Ponce, F., Kuhn, J., Lenartz, D., Mallet, L., Nuttin, B., Real, E., Segalas, C., Schuurman, R., du Montcel, S.T., 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.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IVTR). American Psychiatric Association Press, pp. 108–116.
Angelov, S.D., Dietrich, C., Krauss, J.K., Schwabe, K., 2014. Effect of deep brain stimulation in rats selectively bred for reduced prepulse inhibition. Brain Stimul 7 (4), 595–602.
Berardelli, A., Curra, A., Fabbrini, G., Gilio, F., Manfredi, M., 2003. Pathophysiology of tics and Tourette syndrome. J. Neurol. 250 (7), 781–787.

Blumenthal, T.D., Cuthbert, B.N., Filion, D.L., Hackley, S., Lipp, O.V., van Boxtel, A., 2005. Committee report: guidelines for human startle eyeblink electromyographic studies. Psychophysiology 42 (1), 1–15.
Buse, J., Beste, C., Herrmann, E., Roessner, V., 2016. Neural correlates of altered sensorimotor gating in boys with Tourette Syndrome: a combined EMG/fMRI study. World J. Biol. Psychiatr. : the official journal of the World Federation of Societies of Biological Psychiatry 17 (3), 187–197.
Caine, S.B., Geyer, M.A., Swerdlow, N.R., 1992. Hippocampal modulation of acoustic startle and prepulse inhibition in the rat. Pharmacol. Biochem. Behav. 43 (4), 1201–1208.
Castellanos, F.X., Fine, E.J., Kaysen, D., Marsh, W.L., Rapoport, J.L., Hallett, M., 1996. Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. Biol. Psychiatr. 39 (1), 33–41.
Cox, J.H., Nahar, A., Termine, C., Agosti, M., Balottin, U., Seri, S., Cavanna, A.E., 2019. Social stigma and self-perception in adolescents with tourette syndrome. Adolesc. Health Med. Therapeut. 10, 75–82.
Csomor, P.A., Stadler, R.R., Feldon, J., Yee, B.K., Geyer, M.A., Vollenweider, F.X., 2008. Haloperidol differentially modulates prepulse inhibition and p50 suppression in healthy humans stratified for low and high gating levels. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 33 (3), 497–512.
de Leeuw, A.S., Oranje, B., van Megen, H.J., Kemner, C., Westenberg, H.G., 2010. Sensory gating and sensorimotor gating in medication-free obsessive-compulsive disorder patients. Int. Clin. Psychopharmacol. 25 (4), 232–240.
Della Casa, V., Hofer, I., Weiner, I., Feldon, J., 1998. The effects of smoking on acoustic prepulse inhibition in healthy men and women. Psychopharmacology 137 (4), 362–368.
Denys, D., 2006. Pharmacotherapy of obsessive-compulsive disorder and obsessive- compulsive spectrum disorders. Psychiatr. Clin. 29 (2), 553–584 xi.
Drobes, D.J., MacQueen, D.A., Blank, M.D., Saladin, M.E., Malcolm, R.J., 2013. Effects of intravenous nicotine on prepulse inhibition in smokers and non-smokers: relationship with familial smoking. Psychopharmacology 229 (2), 285–294.
Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., Gonzenbach, S., Angrist, B., Rotrosen, J., 2001. Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology 156 (2–3), 266–272.
Elle, T., Alam, M., Voigt, C., Krauss, J.K., John, N., Schwabe, K., 2020. Deep brain stimulation of the thalamic centromedian-parafascicular nucleus improves behavioural and neuronal traits in a rat model of Tourette. Behav. Brain Res. 378, 112251.
Ellwanger, J., Geyer, M.A., Braff, D.L., 2003. The relationship of age to prepulse inhibition and habituation of the acoustic startle response. Biol. Psychol. 62 (3), 175–195.
Gebhardt, J., Schulz-Juergensen, S., Eggert, P., 2012. Maturation of prepulse inhibition (PPI) in childhood. Psychophysiology 49 (4), 484–488.
Hammer, T.B., Oranje, B., Glenthoj, B.Y., 2007. The effects of imipramine on P50 suppression, prepulse inhibition and habituation of the startle response in humans. Int. J. Neuropsychopharmacol. 10 (6), 787–795.
Hoenig, K., Hochrein, A., Quednow, B.B., Maier, W., Wagner, M., 2005. Impaired prepulse inhibition of acoustic startle in obsessive-compulsive disorder. Biol. Psychiatr. 57 (10), 1153–1158.
Huys, D., Bartsch, C., Koester, P., Lenartz, D., Maarouf, M., Daumann, J., Mai, J.K., Klosterkotter, J., Hunsche, S., Visser-Vandewalle, V., Woopen, C., Timmermann, L., Sturm, V., Kuhn, J., 2016. Motor improvement and emotional stabilization in patients with tourette syndrome after deep brain stimulation of the ventral anterior and ventrolateral motor part of the thalamus. Biol. Psychiatr. 79 (5), 392–401.
Huys, D., Kohl, S., Baldermann, J.C., Timmermann, L., Sturm, V., Visser-Vandewalle, V., Kuhn, J., 2019. Open-label trial of anterior limb of internal capsule-nucleus accumbens deep brain stimulation for obsessive-compulsive disorder: insights gained. J. Neurol. Neurosurg. Psychiatry 90 (7), 805–812.
Jensen, K.S., Oranje, B., Wienberg, M., Glenthoj, B.Y., 2007. The effects of increased central serotonergic activity on prepulse inhibition and habituation of the human startle response. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology 32 (10), 2117–2124.
Kefalopoulou, Z., Zrinzo, L., Jahanshahi, M., Candelario, J., Milabo, C., Beigi, M., Akram, H., Hyam, J., Clayton, J., Kass-Iliyya, L., Silverdale, M., Evans, J.,
Journal of Psychiatric Research 129 (2020) 272–280
Limousin, P., Hariz, M., Joyce, E., Foltynie, T., 2015. Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomised crossover trial. Lancet Neurol. 14 (6), 595–605.
Kodsi, M.H., Swerdlow, N.R., 1995. Prepulse inhibition in the rat is regulated by ventral and caudodorsal striato-pallidal circuitry. Behav. Neurosci. 109 (5), 912–928.
Kohl S., Heekeren K., Klosterkotter J., Kuhn J. Prepulse inhibition in psychiatric disorders – apart from schizophrenia. J. Psychiatr. Res. 47(4), 445-452.

Kohl, S., Gruendler, T.O., Huys, D., Sildatke, E., Dembek, T.A., Hellmich, M., Vorderwulbecke, M., Timmermann, L., Ahmari, S.E., Klosterkoetter, J., Jessen, F., Sturm, V., Visser-Vandewalle, V., Kuhn, J., 2015. Effects of deep brain stimulation on prepulse inhibition in obsessive-compulsive disorder. Transl. Psychiatry 5, e675.
Kumari, V., Checkley, S.A., Gray, J.A., 1996. Effect of cigarette smoking on prepulse inhibition of the acoustic startle reflex in healthy male smokers. Psychopharmacology 128 (1), 54–60.
Kumari, V., Soni, W., Sharma, T., 2001. Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. Hum. Psychopharmacol. 16 (4), 321–326.
Lindemann, C., Krauss, J.K., Schwabe, K., 2012. Deep brain stimulation of the subthalamic nucleus in the 6-hydroxydopamine rat model of Parkinson's disease: effects on sensorimotor gating. Behav. Brain Res. 230 (1), 243–250.
Maciunas, R.J., Maddux, B.N., Riley, D.E., Whitney, C.M., Schoenberg, M.R., Ogrocki, P. J., Albert, J.M., Gould, D.J., 2007. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. J. Neurosurg. 107 (5), 1004–1014.
McIntyre, C.C., Hahn, P.J., 2010. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol. Dis. 38 (3), 329–337.
Miller, E.J., Saint Marie, L.R., Breier, M.R., Swerdlow, N.R., 2010. Pathways from the ventral hippocampus and caudal amygdala to forebrain regions that regulate sensorimotor gating in the rat. Neuroscience 165 (2), 601–611.
Morein-Zamir, S., Fineberg, N.A., Robbins, T.W., Sahakian, B.J., 2010. Inhibition of thoughts and actions in obsessive-compulsive disorder: extending the endophenotype? Psychol. Med. 40, 263–272.
Murray, C.J., Lopez, A.D., 1996. Evidence-based health policy–lessons from the global burden of disease study. Science 274 (5288), 740–743.
Phillips, M.A., Langley, R.W., Bradshaw, C.M., Szabadi, E., 2000. The effects of some antidepressant drugs on prepulse inhibition of the acoustic startle (eyeblink) response and the N1/P2 auditory evoked response in man. J. Psychopharmacol. 14 (1), 40–45.
Posch, D.K., Schwabe, K., Krauss, J.K., Lutjens, G., 2012. Deep brain stimulation of the entopeduncular nucleus in rats prevents apomorphine-induced deficient sensorimotor gating. Behav. Brain Res. 232 (1), 130–136.
Quednow, B.B., Wagner, M., Westheide, J., Beckmann, K., Bliesener, N., Maier, W., Kuhn, K.U., 2006. Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. Biol. Psychiatr. 59 (6), 536–545.
Saint Marie, R.L., Miller, E.J., Breier, M.R., Weber, M., Swerdlow, N.R., 2010. Projections from ventral hippocampus to medial prefrontal cortex but not nucleus accumbens remain functional after fornix lesions in rats. Neuroscience 168 (2), 498–504.
Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, L.R., 1998. Neuroimaging and frontal- subcortical circuitry in obsessive-compulsive disorder. Br. J. Psychiatry Suppl (35), 26–37.
Schellekens, A.F., Grootens, K.P., Neef, C., Movig, K.L., Buitelaar, J.K., Ellenbroek, B., Verkes, R.J., 2010. Effect of apomorphine on cognitive performance and sensorimotor gating in humans. Psychopharmacology 207 (4), 559–569.
Schwabe, K., Krauss, J.K., 2018. What rodent models of deep brain stimulation can teach us about the neural circuit regulation of prepulse inhibition in neuropsychiatric disorders. Schizophr. Res. 198, 45–51.
Steinman, S.A., Ahmari, S.E., Choo, T., Kimeldorf, M.B., Feit, R., Loh, S., Risbrough, V., Geyer, M.A., Steinglass, J.E., Wall, M., Schneier, F.R., Fyer, A.J., Simpson, H.B., 2016. Prepulse inhibition deficits only in females with obsessive-compulsive disorder. Depress. Anxiety 33 (3), 238–246.
Swerdlow, N.R., Caine, S.B., Braff, D.L., Geyer, M.A., 1992. The neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. J. Psychopharmacol. 6 (2), 176–190.
Swerdlow, N.R., Benbow, C.H., Zisook, S., Geyer, M.A., Braff, D.L., 1993. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. Biol. Psychiatr. 33 (4), 298–301.
Swerdlow, N.R., Karban, B., Ploum, Y., Sharp, R., Geyer, M.A., Eastvold, A., 2001. Tactile prepuff inhibition of startle in children with Tourette's syndrome: in search of an "fMRI-friendly" startle paradigm. Biol. Psychiatr. 50 (8), 578–585.
Swerdlow, N.R., Lelham, S.A., Sutherland Owens, A.N., Chang, W.L., Sassen, S.D., Talledo, J.A., 2009. Pramipexole effects on startle gating in rats and normal men. Psychopharmacology 205 (4), 689–698.
Swerdlow, N.R., 2012. Update: studies of prepulse inhibition of startle, with particular relevance to the pathophysiology or treatment of Tourette Syndrome. Neurosci. Biobehav. Rev. 37 (6), 1150–1156.

Vrana, S.R., Calhoun, P.S., McClernon, F.J., Dennis, M.F., Lee, S.T., Beckham, J.C., 2013. Effects of smoking on the acoustic startle response and prepulse inhibition in smokers with and without posttraumatic stress disorder. Psychopharmacology 230 (3), 477–485.
Wan, F.J., Swerdlow, N.R., 1997. The basolateral amygdala regulates sensorimotor gating of acoustic startle in the rat. Neuroscience 76 (3), 715–724.
Welter, M.L., Houeto, J.L., Thobois, S., Bataille, B., Guenot, M., Worbe, Y., Hartmann, A., Czernecki, V., Bardinet, E., Yelnik, J., du Montcel, S.T., Agid, Y., Vidailhet, M., Cornu, P., Tanguy, A., Ansquer, S., Jaafari, N., Poulet, E., Serra, G., Burbaud, P., Cuny, E., Aouizerate, B., Pollak, P., Chabardes, S., Polosan, M., Borg, M.,
Fontaine, D., Giordana, B., Raoul, S., Rouaud, T., Sauvaget, A., Jalenques, I., Karachi, C., Mallet, L., group, S.s., 2017. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. Lancet Neurol. 16 (8), 610–619.
Whiteside, S.P., Port, J.D., Abramowitz, J.S., 2004. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. Psychiatr. Res. 132 (1), 69–79.
Woznica, A.A., Sacco, K.A., George, T.P., 2009. Prepulse inhibition deficits in schizophrenia are modified by smoking status. Schizophr. Res. 112 (1–3), 86–90.
Wynn, J.K., Green, M.F., Sprock, J., Light, G.A., Widmark, C., Reist, C., Erhart, S., Marder, S.R., Mintz, J., Braff, D.L., 2007. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. Schizophr. Res. 95 (1–3), 134–142.
Zebardast, N., Crowley, M.J., Bloch, M.H., Mayes, L.C., Wyk, B.V., Leckman, J.F., Pelphrey, K.A., Swain, J.E., 2013. Brain mechanisms for prepulse inhibition in adults with Tourette syndrome: initial findings. Psychiatr. Res. 214 (1), 33–41.

5. Discussion

We used a clinical, controlled study design to test for influences of DBS on a mechanism essential for the inhibitory control in TS and OCD. What did we learn from our findings?

5.1 Prepulse Inhibition in Tourette Syndrome

We found that PPI of the acoustic startle reflex is deficient in patients with TS. Deficient PPI has already been reported in children with comorbid TS and ADHD, treated with or without pharmacological treatment [2,5,71]. Our findings therefore confirm our proposed hypothesis and represent further evidence for an impairment of the central inhibitory control in adults with TS. Functional imaging studies on the pathophysiology of TS report on altered neural activity and interregional causality in a range of grey matter patterns, including the motor pathway [72]. More specifically, altered structural connectivity of the striatum and thalamus with the supplementary motor area, sensory and primary motor cortices, parietal cortex and paracentral lobule have been implicated [73]. On transmitter basis, a dopaminergic tonic-phasic dysfunction in the basal ganglia with particular relevance of the striatum has been proposed in several human- and animal studies. It has been shown that the phasic dopamine release within the basal ganglia of patients with TS is elevated by 21-50% in comparison to HCs [1,11,74-76]. Cortical malfunctioning has also been shown in PPI studies of patients with TS. Zebardast et al. reported on lower blood oxygen level-dependent activity during PPI in the medial temporal gyrus, the orbitofrontal cortex, the posterior cingulate cortex and the lateral frontal cortex in patients with TS[77]. Congruently, Buse et al. showed correlates between reduced blood oxygen level-dependent activity in the cingulate, postcentral and middle frontal gyri as well as the caudate nucleus and the superior parietal cortex and reduced PPI of patients with TS [1,78]. While the role of the thalamic nuclei remains inconclusive, one might suggest that deficient PPI in patient with TS is caused by (dopaminergic) malfunctioning of the cortex and the striatum [1].

5.2 Prepulse Inhibition in Obsessive Compulsive Disorder

In our study cohort, we did not find evidence for deficient PPI in patients with OCD. Though two studies are in line with our recent findings [79,80], the majority of clinical PPI studies found significant deficiencies of PPI in medicated and unmedicated patients with OCD [81-84]. Neuroimaging studies show abnormally high activity in the orbitofrontal cortex (OFC) and the striatum in patients with OCD [30-32,85]. The NAc core is therefore discussed to mediate abnormalities of PPI in OCD [81]. However, we were not able to confirm our proposed hypothesis and the overall research opinion of an impaired central inhibitory control in adults with OCD, which could be caused by the rather small patient cohort.

5.3 Effect of Deep Brain Stimulation on Prepulse Inhibition

DBS of the thalamic nuclei had no major effect on the amount of PPI in patients with TS. To our knowledge, we are the first centre to conduct a clinical study on this matter. Keeping in mind our rather small cohort, our results hint to no influence of the thalamus on PPI [1]. This is congruent to the fact that in the literature to date, there is no evidence of a modulating effect of the thalamus itself on PPI circuits. However, a functional magnetic resonance imaging (fMRI) study indicated that in patients with TS, stimulation in the thalamus increased blood oxygen level-dependent signals in the NAc [86]. Furthermore, Angelov et al. showed that in rats that were selectively bred for reduced PPI, DBS of the thalamus improved PPI levels [87]. It is assumed that DBS modulates whole networks of neurons rather than the specific target. Furthermore, it has been hypothesized that over time, DBS induces long-term changes of neuroplasticity [88]. We therefore need to consider the possibility that data of our patients with TS did not differ more significantly between off-sessions and on-sessions because of altered (corrected) neuroplasticity as a treatment effect. Thinking one step further, this could mean that DBS altered PPI in on- and off-sessions likewise. A conclusion concerning this matter requires an analysis of pre-operation measurements of our patients. However, the study of PPI in children with comorbid ADHD and TS of Castellanos et al. revealed PPI levels comparable to the levels of our patients with TS treated with DBS in off-sessions of about 20% [71]. Overall, we think that an effect of DBS on PPI cannot be ruled out by our data with small sample sizes.

DBS of the NAc had no effect on PPI in patients with OCD. Some translational animal models are in line with this finding, such as Angelov et al. who found no significant increase of PPI by DBS of the nucleus accumbens in animal models [1,87]. So far, one study concerning this matter in humans has been published by our study department in the article Kohl et al [89]. In this study, we assessed the amount of PPI in patients with OCD and DBS treatment, patients with OCD and pharmacological treatment and HC. PPI was significantly lower in patients with DBS treatment when the stimulation was switched off than in HC. When the stimulation was switched on, the amount of PPI of patients with OCD did not differ significantly from HC. Kohl concluded that PPI was modified by the stimulation [89]. The NAc is hypothesized to have a direct inhibitory effect on PPI. By successfully modulating obsessive-compulsive symptoms, a positive effect of Nac-DBS on deficient PPI appears reasonable. Our study design [1] has striking analogies with our former study of Kohl et al. However, there were differences in the study samples. First, the time since surgery differed as the cohort of the present study received DBS for approximately one year before being included in the study, whereas the cohort of Kohl et al. was stimulated for on average two years [89]. However, our analysis found no effect of time since surgery on the study results. Other differences in the two studies include the mean age of patients and the smoking status, which will both be addressed in the following limitations.

5.4 Limitations

5.4.1. Effect of nicotine on Prepulse Inhibition

Nicotine binds to central nicotinic cholinergic receptors and thereby releases various neurotransmitters including dopamine. Increased dopamine levels in the striatum and frontal cortex match with neuroimaging findings of acutely increased activity throughout the CSTC loops following nicotine administration [90]. An enhancing effect of nicotine on the amount of PPI of the acoustic startle has been demonstrated in healthy subjects [91-94] as well as in patients with psychiatric disorders, such as schizophrenia [95-97]. The percentage of smokers differed among the analysed cohorts in our study. Two patients with TS smoked whereas only one HC smoked. Two patients with OCD smoked whereas three HC smoked. However, our analyses indicated that our data was not biased by the smoking condition of our patients and HC. Still, one should consider that the dopamine releasing effect of nicotine in HC may not be easily translated to patients with TS and OCD: as stated earlier, TS is associated with an increased dopamine release. Furthermore, abnormalities of the dopaminergic system have been described in patients with OCD. Little is known about the modulating effects of the dopaminergic system in patients with TS and OCD following nicotine administration. However, a small amount of studies and case reports published around the turn of the century have reported on favourable effects of nicotine on tic severity in patients with TS [98-100] and two publications described favourable effects on YBOCS scores in four patients with OCD [101,102]. Though the exact effect of nicotine on the dopaminergic system in our patient cohorts and on their PPI levels remain uncertain, we cannot exclude the possibility of nicotine to bias the observed data [1].

5.4.2. Effect of age on Prepulse Inhibition

Furthermore, the literature to date suggests that age may influence PPI. It has been proposed that PPI matures in childhood and declines with age [103]. However, the study of Ellwanger et al. found a U-shape of PPI with the peak at the age of 41.6 years and reduced levels of participants older and younger [1,104]. Still, there is no sufficient knowledge on how and why aging may influence PPI. In our study, the TS cohort and its HC group were younger than the OCD cohort and its HC group (TS age M = 26,3 years, TS-HC age M = 27,8 years, OCD age M = 48,4 years, OCD-HC age M = 46,29 years). We observed that PPI was lower in the younger patient- and HC groups than in the older patient- and HC groups. Furthermore, patients with OCD of the cohort in Kohl et al. [89] were slightly younger than patients in the present OCD cohort, hence exhibiting lower PPI values. Our data therefore may support the hypothesis of an increase of PPI from young- to middle-aged patients [1].

5.4.3. Effect of gender on Prepulse Inhibition

In 2016, Steinman et al. conducted a PPI study in a large cohort of patients with OCD (N=45) compared to HC. Interestingly, they found PPI to be deficient only in females with OCD compared to HC [83]. Taking this into account, we conducted another ANCOVA and included gender as a covariate. However, results did also not indicate an influence on our results. Nevertheless, female ovarian steroid hormones, including progesterone and estradiol, have been implicated to impair PPI. In a study of Bannbers et al., cycling healthy women exhibited lower levels of PPI than postmenopausal healthy women [105]. This may bias our study in two different ways as it may either a) be in line with the earlier discussed findings of enhanced PPI values in middle-aged humans or b) implicate possible differences in PPI based on the measurement in different phases of the hormonal cycles [1].

5.4.4. Effect of medication on Prepulse Inhibition

Furthermore, an influence of medication on the amount of PPI has to be taken into account. In our cohort of patients with TS and OCD, the use of anti-dopaminergic and serotoninergic pharmacological agents was common. It has been shown that particularly dopamine influences the mechanism of PPI. Congruently, clinical studies report on lowered PPI following administration of typical and atypical antipsychotics in patients with schizophrenia and healthy subjects [5,106,107]. However, Wynn et al. reported on enhanced PPI following the administration of the atypical antipsychotic agent olanzapine in patients with schizophrenia [108]. In 2007, Hammer et al. reported on significantly decreased PPI following administration of the tricyclic antidepressant imipramine in healthy subjects [109]. However, other clinical studies rather indicate no relevant influences of serotoninergic medication on the amount of PPI in healthy subjects [110-112]. Thus, medication may modulate the amount of PPI. Still, the question remains if these agents influence the amount of PPI, though they are insufficient to reduce symptoms in our patients, who per definition are all considered treatment refractory to such approaches[1].

5.4.5. Further Limitations

In addition to the fact that the exact biasing effect of nicotine, age, gender and medication on PPI and DBS are unknown, our PPI study has further limitations. DBS remains an augmentation strategy for treatment resistant psychiatric patients, which is why the analysed patient cohorts are small. Also, stimulation parameters were chosen based on best clinical results so that they vary among the cohorts. With most of the seen effects not reaching statistical significance, science is in need for larger cohorts to shed further light on the effect of thalamus- and NAc-DBS on PPI. Finally, patients were tested after 6 or 12 months of active stimulation rather than at a consistent follow-up point. Therefore, the possibility of further effects between these two follow-up points cannot be ruled out [1].

6. References

1. Schleyken S, Baldermann J, Huys D, et al. Deep brain stimulation and sensorimotor gating in tourette syndrome and obsessive-compulsive disorder. *Journal of psychiatric research* 2020; **129**: 272-80.
2. Kohl S, Heekeren K, Klosterkotter J, Kuhn J. Prepulse inhibition in psychiatric disorders--apart from schizophrenia. *Journal of psychiatric research* 2013; **47**(4): 445-52.
3. Bernard JA, Russell CE, Newberry RE, Goen JR, Mittal VA. Patients with schizophrenia show aberrant patterns of basal ganglia activation: Evidence from ALE meta-analysis. *Neuroimage Clin* 2017; **14**: 450-63.
4. Swerdlow NR, Caine SB, Braff DL, Geyer MA. The neural substrates of sensorimotor gating of the startle reflex: a review of recent findings and their implications. *Journal of psychopharmacology (Oxford, England)* 1992; **6**(2): 176-90.
5. Swerdlow NR. Update: studies of prepulse inhibition of startle, with particular relevance to the pathophysiology or treatment of Tourette Syndrome. *Neuroscience and biobehavioral reviews* 2013; **37**(6): 1150-6.
6. Falkai P, Wittchen H, Döpfner M, et al. Tic-Störungen. Diagnostische Kriterien DSM-5. 5 ed. Göttingen: Hogrefe Verlag; 2015: 108 - 15.
7. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol* 2000; **42**(7): 436-47.
8. Berardelli A, Curra A, Fabbrini G, Gilio F, Manfredi M. Pathophysiology of tics and Tourette syndrome. *J Neurol* 2003; **250**(7): 781-7.
9. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989; **28**(4): 566-73.
10. Ludolph AG, Roessner V, Munchau A, Muller-Vahl K. Tourette syndrome and other tic disorders in childhood, adolescence and adulthood. *Dtsch Arztebl Int* 2012; **109**(48): 821-288.
11. Buse J, Schoenefeld K, Munchau A, Roessner V. Neuromodulation in Tourette syndrome: dopamine and beyond. *Neuroscience and biobehavioral reviews* 2013; **37**(6): 1069-84.
12. Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. *Eur Child Adolesc Psychiatry* 2011; **20**(4): 173-96.
13. Cox JH, Nahar A, Termine C, et al. Social stigma and self-perception in adolescents with tourette syndrome. *Adolesc Health Med Ther* 2019; **10**: 75-82.
14. Yates R, Edwards K, King J, et al. Habit reversal training and educational group treatments for children with tourette syndrome: A preliminary randomised controlled trial. *Behav Res Ther* 2016; **80**: 43-50.
15. McGuire JF, Piacentini J, Brennan EA, et al. A meta-analysis of behavior therapy for Tourette Syndrome. *Journal of psychiatric research* 2014; **50**: 106-12.
16. Roessner V, Rothenberger A, Rickards H, Hoekstra PJ. European clinical guidelines for Tourette syndrome and other tic disorders. *Eur Child Adolesc Psychiatry* 2011; **20**(4): 153-4.
17. Huys D, Hardenacke K, Poppe P, Bartsch C, Baskin B, Kuhn J. Update on the role of antipsychotics in the treatment of Tourette syndrome. *Neuropsychiatr Dis Treat* 2012; **8**: 95-104.
18. Quezada J, Coffman KA. Current Approaches and New Developments in the Pharmacological Management of Tourette Syndrome. *CNS Drugs* 2018; **32**(1): 33-45.
19. Nguyen V, Tiemann D, Park E, Salehi A. Alpha-2 Agonists. *Anesthesiol Clin* 2017; **35**(2): 233-45.
20. Roth J. The colorful spectrum of Tourette syndrome and its medical, surgical and behavioral therapies. *Parkinsonism & related disorders* 2018; **46 Suppl 1**: S75-s9.
21. Stein DJ, Costa DLC, Lochner C, et al. Obsessive-compulsive disorder. *Nat Rev Dis Primers* 2019; **5**(1): 52.
22. Falkai P, Wittchen H, Döpfner M, et al. Zwangsstörungen. Diagnostische Kriterien DSM-5. 1 ed. Göttingen: Hogrefe Verlag; 2015: 322 - 30.
23. Hirschtritt ME, Bloch MH, Mathews CA. Obsessive-Compulsive Disorder: Advances in Diagnosis and Treatment. *JAMA* 2017; **317**(13): 1358-67.
24. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**(6): 617-27.
25. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989; **46**(11): 1006-11.
26. Figee M, Wielaard I, Mazaheri A, Denys D. Neurosurgical targets for compulsivity: what can we learn from acquired brain lesions? *Neuroscience and biobehavioral reviews* 2013; **37**(3): 328-39.

27. Kuelz AK, Hohagen F, Voderholzer U. Neuropsychological performance in obsessive-compulsive disorder: a critical review. *Biol Psychol* 2004; **65**(3): 185-236.
28. Shin NY, Lee TY, Kim E, Kwon JS. Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. *Psychol Med* 2014; **44**(6): 1121-30.
29. Nakao T, Okada K, Kanba S. Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. *Psychiatry Clin Neurosci* 2014; **68**(8): 587-605.
30. Benkelfat C, Nordahl TE, Semple WE, King AC, Murphy DL, Cohen RM. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. Patients treated with clomipramine. *Arch Gen Psychiatry* 1990; **47**(9): 840-8.
31. Baxter LR, Jr., Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. *Arch Gen Psychiatry* 1987; **44**(3): 211-8.
32. Goodman WK, Grice DE, Lapidus KA, Coffey BJ. Obsessive-compulsive disorder. *Psychiatr Clin North Am* 2014; **37**(3): 257-67.
33. Pogarell O, Hamann C, Popperl G, et al. Elevated brain serotonin transporter availability in patients with obsessive-compulsive disorder. *Biological psychiatry* 2003; **54**(12): 1406-13.
34. Hesse S, Muller U, Lincke T, et al. Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder. *Psychiatry research* 2005; **140**(1): 63-72.
35. Simpson HB, Slifstein M, Bender J, Jr., et al. Serotonin 2A receptors in obsessive-compulsive disorder: a positron emission tomography study with [11C]MDL 100907. *Biological psychiatry* 2011; **70**(9): 897-904.
36. Skapinakis P, Caldwell D, Hollingworth W, et al. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. *Health Technol Assess* 2016; **20**(43): 1-392.
37. Sangkuhl K, Klein TE, Altman RB. Selective serotonin reuptake inhibitors pathway. *Pharmacogenet Genomics* 2009; **19**(11): 907-9.
38. Latendresse G, Elmore C, Deneris A. Selective Serotonin Reuptake Inhibitors as First-Line Antidepressant Therapy for Perinatal Depression. *J Midwifery Womens Health* 2017; **62**(3): 317-28.
39. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. *Psychopharmacology* 1994; **114**(4): 559-65.
40. Green JP, Maayani S. Tricyclic antidepressant drugs block histamine H2 receptor in brain. *Nature* 1977; **269**(5624): 163-5.
41. Xu J, Hao Q, Qian R, et al. Optimal Dose of Serotonin Reuptake Inhibitors for Obsessive-Compulsive Disorder in Adults: A Systematic Review and Dose-Response Meta-Analysis. *Front Psychiatry* 2021; **12**: 717999.
42. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB, American Psychiatric A. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry* 2007; **164**(7 Suppl): 5-53.
43. Menchon JM, van Ameringen M, Dell'Osso B, et al. Standards of care for obsessive-compulsive disorder centres. *Int J Psychiatry Clin Pract* 2016; **20**(3): 204-8.
44. Graat I, Figee M, Denys D. The application of deep brain stimulation in the treatment of psychiatric disorders. *Int Rev Psychiatry* 2017; **29**(2): 178-90.
45. Baldermann JC, Melzer C, Zapf A, et al. Connectivity Profile Predictive of Effective Deep Brain Stimulation in Obsessive-Compulsive Disorder. *Biological psychiatry* 2019; **85**(9): 735-43.
46. Baldermann JC, Kuhn J, Schuller T, et al. Thalamic deep brain stimulation for Tourette Syndrome: A naturalistic trial with brief randomized, double-blinded sham-controlled periods. *Brain Stimul* 2021; **14**(5): 1059-67.
47. Ackermans L, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain* 2011; **134**(Pt 3): 832-44.
48. Baldermann JC, Kuhn J, Schüller T, et al. Thalamic deep brain stimulation for Tourette Syndrome: A naturalistic trial with brief randomized, double-blinded sham-controlled periods. *Brain Stimul* 2021; **14**(5): 1059-67.
49. Schwabe K, Krauss JK. What rodent models of deep brain stimulation can teach us about the neural circuit regulation of prepulse inhibition in neuropsychiatric disorders. *Schizophr Res* 2018; **198**: 45-51.
50. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol* 2004; **115**(6): 1239-48.
51. Aumüller G, Aust G, Engele J, et al. 2. ZNS - funktionelle Systeme. Duale Reihe Anatomie. 3 ed. Stuttgart: Georg Thieme Verlag KG; 2014: 1181 - 261.

52. Schmidt R, Lang F, Heckmann M. 7.6 Optimierung von Zielbewegungen durch die Basalganglien und 7.7 Funktionelle Organisation der motorischen Rindenfelder. Physiologie des Menschen mit Pathophysiologie. 31 ed. Heidelberg: Springer Medizin Verlag; 2010: 148 - 62.
53. Schuenke M, Schulte E, Schumacher U, Voll M, Wesker K. 6.9 Nuclei basales (Basalkerne). Prometheus Lernatlas der Anatomie: Kopf, Hals und Neuroanatomie. 3 ed. Stuttgart: Georg Thieme Verlag; 2012: 326 - 7.
54. Saxena S, Bota RG, Brody AL. Brain-behavior relationships in obsessive-compulsive disorder. *Semin Clin Neuropsychiatry* 2001; **6**(2): 82-101.
55. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989; **12**(10): 366-75.
56. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 1996; **50**(4): 381-425.
57. Bystritsky A, Liberman RP, Hwang S, et al. Social functioning and quality of life comparisons between obsessive-compulsive and schizophrenic disorders. *Depression and anxiety* 2001; **14**(4): 214-8.
58. Schuenke M, Schulte E, Schumacher U, Voll M, Wesker K. 7.4 Thalamus: Kerngebiete und 7.5 Thalamus: Projektionen der Thalamuskerne. Prometheus Lernatlas der Anatomie: Kopf, Hals und Neuroanatomie. 3 ed. Stuttgart: Georg Thieme Verlag; 2012: 334 - 7.
59. Schroeder H. Anatomie des Menschen - Ein Internetatlas des Zentrums Anatomie der Universitaet zu Koeln. 2015. https://www.anatomiedesmenschen.uni-koeln.de/netscape/neuro/frontal/01_atlas.htm (accessed 15.12.2019 2019).
60. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol Dis* 2010; **38**(3): 329-37.
61. McCracken CB, Grace AA. Nucleus accumbens deep brain stimulation produces region-specific alterations in local field potential oscillations and evoked responses in vivo. *J Neurosci* 2009; **29**(16): 5354-63.
62. Figee M, Luigjes J, Smolders R, et al. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci* 2013; **16**(4): 386-7.
63. van Dijk A, Klompmakers AA, Feenstra MG, Denys D. Deep brain stimulation of the accumbens increases dopamine, serotonin, and noradrenaline in the prefrontal cortex. *J Neurochem* 2012; **123**(6): 897-903.
64. Figee M, de Koning P, Klaassen S, et al. Deep brain stimulation induces striatal dopamine release in obsessive-compulsive disorder. *Biological psychiatry* 2014; **75**(8): 647-52.
65. Vernaleken I, Kuhn J, Lenartz D, et al. Bithalamical deep brain stimulation in tourette syndrome is associated with reduction in dopaminergic transmission. *Biological psychiatry* 2009; **66**(10): e15-7.
66. Baldermann JC, Schuller T, Huys D, et al. Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis. *Brain Stimul* 2016; **9**(2): 296-304.
67. Alonso P, Cuadras D, Gabriels L, et al. Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Meta-Analysis of Treatment Outcome and Predictors of Response. *PloS one* 2015; **10**(7): e0133591.
68. Kohl S, Baldermann JC. Progress and challenges in deep brain stimulation for obsessive-compulsive disorder. *Pharmacol Ther* 2018; **186**: 168-75.
69. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome: The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. *JAMA Neurol* 2018; **75**(3): 353-9.
70. Welter ML, Houeto JL, Thobois S, et al. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. *Lancet Neurol* 2017; **16**(8): 610-9.
71. Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M. Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. *Biological psychiatry* 1996; **39**(1): 33-41.
72. Wang Z, Maia TV, Marsh R, Colibazzi T, Gerber A, Peterson BS. The neural circuits that generate tics in Tourette's syndrome. *Am J Psychiatry* 2011; **168**(12): 1326-37.
73. Worbe Y, Marrakchi-Kacem L, Lecomte S, et al. Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome. *Brain* 2015; **138**(Pt 2): 472-82.
74. Singer HS, Szymanski S, Giuliano J, et al. Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. *Am J Psychiatry* 2002; **159**(8): 1329-36.
75. Wong DF, Brasic JR, Singer HS, et al. Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2008; **33**(6): 1239-51.
76. Steeves TD, Ko JH, Kideckel DM, et al. Extrastriatal dopaminergic dysfunction in tourette syndrome. *Ann Neurol* 2010; **67**(2): 170-81.

77. Zebardast N, Crowley MJ, Bloch MH, et al. Brain mechanisms for prepulse inhibition in adults with Tourette syndrome: initial findings. *Psychiatry research* 2013; **214**(1): 33-41.
78. Buse J, Beste C, Herrmann E, Roessner V. Neural correlates of altered sensorimotor gating in boys with Tourette Syndrome: A combined EMG/fMRI study. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry* 2016; **17**(3): 187-97.
79. de Leeuw AS, Oranje B, van Megen HJ, Kemner C, Westenberg HG. Sensory gating and sensorimotor gating in medication-free obsessive-compulsive disorder patients. *International clinical psychopharmacology* 2010; **25**(4): 232-40.
80. Pittenger C, Adams TG, Jr., Gallezot JD, et al. OCD is associated with an altered association between sensorimotor gating and cortical and subcortical 5-HT1b receptor binding. *Journal of affective disorders* 2016; **196**: 87-96.
81. Hoenig K, Hochrein A, Quednow BB, Maier W, Wagner M. Impaired prepulse inhibition of acoustic startle in obsessive-compulsive disorder. *Biological psychiatry* 2005; **57**(10): 1153-8.
82. Ahmari SE, Risbrough VB, Geyer MA, Simpson HB. Prepulse Inhibition Deficits in Obsessive-Compulsive Disorder are More Pronounced in Females. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2016; **41**(13): 2963-4.
83. Steinman SA, Ahmari SE, Choo T, et al. PREPULSE INHIBITION DEFICITS ONLY IN FEMALES WITH OBSESSIVE-COMPULSIVE DISORDER. *Depression and anxiety* 2016; **33**(3): 238-46.
84. Ahmari SE, Risbrough VB, Geyer MA, Simpson HB. Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2012; **37**(5): 1216-23.
85. Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry research* 2004; **132**(1): 69-79.
86. Jo HJ, McCairn KW, Gibson WS, et al. Global network modulation during thalamic stimulation for Tourette syndrome. *Neuroimage Clin* 2018; **18**: 502-9.
87. Angelov SD, Dietrich C, Krauss JK, Schwabe K. Effect of deep brain stimulation in rats selectively bred for reduced prepulse inhibition. *Brain Stimul* 2014; **7**(4): 595-602.
88. Ashkan K, Rogers P, Bergman H, Ughratdar I. Insights into the mechanisms of deep brain stimulation. *Nat Rev Neurol* 2017; **13**(9): 548-54.
89. Kohl S, Gruendler TO, Huys D, et al. Effects of deep brain stimulation on prepulse inhibition in obsessive-compulsive disorder. *Translational psychiatry* 2015; **5**: e675.
90. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol* 2009; **49**: 57-71.
91. Kumari V, Checkley SA, Gray JA. Effect of cigarette smoking on prepulse inhibition of the acoustic startle reflex in healthy male smokers. *Psychopharmacology* 1996; **128**(1): 54-60.
92. Della Casa V, Hofer I, Weiner I, Feldon J. The effects of smoking on acoustic prepulse inhibition in healthy men and women. *Psychopharmacology* 1998; **137**(4): 362-8.
93. Duncan E, Madonick S, Chakravorty S, et al. Effects of smoking on acoustic startle and prepulse inhibition in humans. *Psychopharmacology* 2001; **156**(2-3): 266-72.
94. Drobes DJ, MacQueen DA, Blank MD, Saladin ME, Malcolm RJ. Effects of intravenous nicotine on prepulse inhibition in smokers and non-smokers: relationship with familial smoking. *Psychopharmacology* 2013; **229**(2): 285-94.
95. Kumari V, Soni W, Sharma T. Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Hum Psychopharmacol* 2001; **16**(4): 321-6.
96. Woznica AA, Sacco KA, George TP. Prepulse inhibition deficits in schizophrenia are modified by smoking status. *Schizophr Res* 2009; **112**(1-3): 86-90.
97. Vrana SR, Calhoun PS, McClernon FJ, Dennis MF, Lee ST, Beckham JC. Effects of smoking on the acoustic startle response and prepulse inhibition in smokers with and without posttraumatic stress disorder. *Psychopharmacology* 2013; **230**(3): 477-85.
98. Silver AA, Shytle RD, Philipp MK, Wilkinson BJ, McConville B, Sanberg PR. Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. *J Clin Psychiatry* 2001; **62**(9): 707-14.
99. Howson AL, Batth S, Ilivitsky V, et al. Clinical and attentional effects of acute nicotine treatment in Tourette's syndrome. *Eur Psychiatry* 2004; **19**(2): 102-12.
100. Orth M, Amann B, Robertson MM, Rothwell JC. Excitability of motor cortex inhibitory circuits in Tourette syndrome before and after single dose nicotine. *Brain* 2005; **128**(Pt 6): 1292-300.
101. Lundberg S, Carlsson A, Norfeldt P, Carlsson ML. Nicotine treatment of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28**(7): 1195-9.
102. Salin-Pascual RJ, Basanez-Villa E. Changes in compulsion and anxiety symptoms with nicotine transdermal patches in non-smoking obsessive-compulsive disorder patients. *Rev Invest Clin* 2003; **55**(6): 650-4.

103. Gebhardt J, Schulz-Juergensen S, Eggert P. Maturation of prepulse inhibition (PPI) in childhood. *Psychophysiology* 2012; **49**(4): 484-8.
104. Ellwanger J, Geyer MA, Braff DL. The relationship of age to prepulse inhibition and habituation of the acoustic startle response. *Biol Psychol* 2003; **62**(3): 175-95.
105. Bannbers E, Kask K, Wikstrom J, Sundstrom Poromaa I. Lower levels of prepulse inhibition in luteal phase cycling women in comparison with postmenopausal women. *Psychoneuroendocrinology* 2010; **35**(3): 422-9.
106. Csomor PA, Stadler RR, Feldon J, Yee BK, Geyer MA, Vollenweider FX. Haloperidol differentially modulates prepulse inhibition and p50 suppression in healthy humans stratified for low and high gating levels. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2008; **33**(3): 497-512.
107. Quednow BB, Wagner M, Westheide J, et al. Sensorimotor gating and habituation of the startle response in schizophrenic patients randomly treated with amisulpride or olanzapine. *Biological psychiatry* 2006; **59**(6): 536-45.
108. Wynn JK, Green MF, Sprock J, et al. Effects of olanzapine, risperidone and haloperidol on prepulse inhibition in schizophrenia patients: a double-blind, randomized controlled trial. *Schizophr Res* 2007; **95**(1-3): 134-42.
109. Hammer TB, Oranje B, Glenthoj BY. The effects of imipramine on P50 suppression, prepulse inhibition and habituation of the startle response in humans. *Int J Neuropsychopharmacol* 2007; **10**(6): 787-95.
110. Jensen KS, Oranje B, Wienberg M, Glenthoj BY. The effects of increased central serotonergic activity on prepulse inhibition and habituation of the human startle response. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2007; **32**(10): 2117-24.
111. Phillips MA, Langley RW, Bradshaw CM, Szabadi E. The effects of some antidepressant drugs on prepulse inhibition of the acoustic startle (eyeblink) response and the N1/P2 auditory evoked response in man. *Journal of psychopharmacology (Oxford, England)* 2000; **14**(1): 40-5.
112. Abel KM, Allin M, van Amelsvoort T, Hemsley D, Geyer MA. The indirect serotonergic agonist d-fenfluramine and prepulse inhibition in healthy men. *Neuropharmacology* 2007; **52**(4): 1088-94.

7. Appendix

7.1 List of Figures