Tourette Syndrome: Electrophysiological Insights and Prospects for Deep Brain Stimulation

Inaugural Dissertation

zur

Erlangung des Doktorgrades
philosophiae doctor (PhD) in Health Sciences
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von

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Digital Express 24, Köln

2024

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Datum der Mündlichen Prüfung:	11.06.2024

Acknowledgements

First and foremost, I wish to thank my supervisor, Pablo Andrade, for his unwavering support throughout this transformative journey. Your understanding of my individual needs, your trust, and constant encouragement have been indispensable. You have opened doors for me that I never have imagined, offering opportunities for exceptional personal and professional development. For similar reasons, I express my heartfelt appreciation to Veerle Visser-Vandewalle, whose example of strength and fearlessness are truly inspiring.

A profound thank you goes out to the entire team that made this work possible: Juan Carlos Baldermann, Thomas Schüller, Petra Heiden, Thibaut Sesia, Anna-Katharina Zur Mühlen, and Annika Sauter. Your intellectual contributions, wealth of experience, and engaging scientific exchanges, along with the fun we had during recordings, have significantly enriched my past years. I am equally indebted to Daniel Huys and Jens Kuhn, who, before I started my PhD, provided me the opportunity to lay the foundation for my academic pursuits.

Most importantly, I would like to express my deepest gratitude to all the participants who invested their time and effort in our studies. I especially thank the patients, whose trust, openness, and shared experiences provided me with invaluable insights. These unique experiences have allowed me to transcend conventional boundaries, deepen my understanding of the collected data, and generate new research questions that will undoubtedly contribute to future research endeavors. A special thank you goes to the Life Ticcer e.V., especially Fabiene Wengert, for their vital work and for inviting me to their Tourette-camp – a transcendent experience so much far beyond the clinical research routine.

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List of Abbreviations

TS	Tourette syndrome
PMU	Premonitory urge
ADHD	Attention deficit hyperactivity disorder
OCD	Obsessive-compulsive disorder
CBGTC	Cortico-basal ganglia-thalamo-cortical circuits
BG	Basal ganglia
STN	Subthalamic nucleus
GPi	Globus pallidus internus
amGPi	Anteromedial globus pallidus internus
pvlGPi	Posteroventrolateral globus pallidus internus
GPe	Globus pallidus externus
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
fMRI	Functional magnetic resonance imaging
DTI	Diffusion tensor imaging
SMA	Supplementary motor area
ACC	Anterior cingulate cortex
TEC	Theory of event coding
CBIT	Cognitive Behavioral Intervention for Tics
HRT	Habit Reversal Training
DBS	Deep brain stimulation
IPG	Implanted pulse generator
VTA	Volume of tissue activated
ET	Essential tremor
PD	Parkinson’s disease
LFP	Local field potential
FDA	US Food and Drug Administration
RCT	Randomized controlled and double-blinded trials
FU	Follow-up
CM-Spv-Voi	Centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus complex

CM-Voi	Centromedian nucleus–nucleus ventrooralis internus
CM-Pf	Centromedian nucleus–parafascicular
VA/VL	Ventral anterior/ventrolateral thalamus
ALIC/NAc	Anterior limb of internal capsule/nucleus accumbens
EEG	Electroencephalography
ERP	Event-related potential
ICA	Independent component analysis
CSD	Current source density
RIDE	Residue iteration decomposition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
YGTSS	Yale Global Tic Severity Scale
mRVRS	Modified Rush Video-Based Tic Rating Scale
PUTS	Premonitory Urge for Tics Scale
OCI-R	Revised Obsessive-Compulsive Inventory
BDI	Becks Depression Inventory
BDI-II	Beck Depression Inventory - Version II
WURS-K	Wender Utah Rating Scale
YBOCS	Yale-Brown Obsessive Compulsive Scale
CTI	Cue-target interval
RCI	Response-cue interval
TMS	Transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
VNS	Vagus nerve stimulation
RT	Reaction time
SD	Standard deviation
Mdn	Median
IQR	Interquartile range
CI	Confidence interval
FDR	False discovery rate
BIC	Bayesian information criterion

Zusammenfassung

Tourette-Syndrom (TS) ist eine neuropsychiatrische Erkrankung, die sich durch vokale und motorische Tics kennzeichnet. Die zugrunde liegende Pathophysiologie des TS ist unvollständig verstanden. Kognitive Veränderungen im TS und deren neuronale Korrelate können wertvolle Einblicke in die zugrunde liegende Pathophysiologie bieten. Die Tiefenhirnstimulation (THS) ist ein vielversprechender Behandlungsweg für Patienten mit refraktärem TS. Die optimale Auswahl der THS-Zielregion ist jedoch aufgrund unklarer Unterschiede der zielbezogenen klinischen Effekten und Wirkmechanismen umstritten.

Das primäre Ziel war eine umfassende elektrophysiologische Untersuchung kognitiver Prozesse, die möglicherweise zur Tic Entstehung beitragen. Unter Verwendung des „Task Switching"-Paradigmas wurden verschiedene kognitive Prozesse untersucht, um die komplexen kognitiven Grundlagen des TS und deren neurophysiologische Korrelate zu verstehen. Während kognitive Kontrollprozesse sowie Prozesse zur Kopplung von Perzeptionen unverändert erschienen, zeigten Patienten deutlich veränderte neuronale Prozesse, die der Bindung von Perzeption und Handlung (engl. *Perception-action binding*) zugrunde liegen. Dies unterstreicht die Schlüsselrolle des Zusammenspiels zwischen Perzeptionen wie dem Vorgefühl und motorischen Handlungen wie den Tics im TS.

Das sekundäre Ziel bestand darin, die Wirksamkeit der THS im TS zu bewerten und zielbezogene klinische Effekte mit Hilfe einer systematischen Übersicht und Meta-analyse zu vergleichen. Die Ergebnisse zeigen, dass die THS im Allgemeinen eine wirksame therapeutische Option für TS ist, wobei die pallidale im Vergleich zur thalamischen THS höhere Verbesserungsraten aufweist. Diese Ergebnisse sprechen jedoch nicht für die Bevorzugung eine Zielregion gegenüber einer anderen. Vielmehr betonen sie, dass keine einzelne THS-Zielregion der Heterogenität im TS gerecht werden kann. Daher ist die personalisierte Auswahl der THS-Zielregion, basierend auf den spezifischen Symptomen und Merkmalen jedes Patienten, unerlässlich. Um diesen personalisierten Präzisionsansatz zu verwirklichen, ist ein tieferes Verständnis von Biomarkern der den Tics zugrunde liegenden pathologischen neurophysiologischen Mechanismen erforderlich. In dieser Dissertation werden potenzielle Biomarker für die gezielte Neuromodulation ausführlich erörtert.

Zusammenfassend stellt diese Dissertation einen entscheidenden Schritt für ein fortgeschrittenen Verständnisses der Pathophysiologie des TS und der Möglichkeiten der THS dar. Sie weist den Weg zu personalisierten, stimulationsbasierten Behandlungsstrategien und unterstreicht den Bedarf an weiterer Forschung.

Summary

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the presence of motor and vocal tics. The underlying pathophysiology of TS remains incompletely understood. Cognitive alterations in TS and their neural correlates can provide valuable insights into the clinical features and underlying pathophysiology. Deep Brain Stimulation (DBS) emerges a promising treatment avenue for patients with treatment-refractory TS. However, optimal DBS target selection remains controversial due to unclear differences in target-specific clinical effects and mechanisms of action.

The primary objective of this dissertation was to conduct an extensive electrophysiological investigation into cognitive processes potentially contributing to tic occurrence. Using the task switching paradigm, various cognitive processes were examined, unraveling the complex cognitive foundations of TS and their neurophysiological correlates. While cognitive control and perceptual binding processes appear unchanged, individuals with TS exhibit significant alterations in the neural processes underlying perception-action binding. This highlights the pivotal role of the interplay between perceptual processes, such as the premonitory urge, and motor actions, such as tics, in understanding tic occurrence.

The secondary objective focused on evaluating the efficacy of DBS in TS and systematically comparing target-specific clinical effects through a systematic review and meta-analysis. The findings reveal that DBS is generally an effective therapeutic option for TS, with pallidal DBS yielding the highest rates of improvement when compared to thalamic DBS. However, these results do not favor one target over another. Instead, they emphasize that no single DBS target can address the heterogeneous phenotypes and comorbidities in TS. Thus, personalized DBS target selection tailored to each patient's specific symptoms and characteristics becomes essential. Achieving this personalized precision approach requires a deeper understanding of biomarkers related to the underlying neurophysiological mechanisms driving tics in TS. This dissertation extensively discusses potential biomarkers for neuromodulation, encompassing neural mechanisms related to urges, perception-action binding, tic initiation, and tic control.

In conclusion, this dissertation represents a crucial step towards an advanced comprehension of TS pathophysiology and the applications of DBS, thereby illuminating the path towards personalized stimulation-based treatment strategies, underlining the need for further research.

1. Theoretical Section

1.1 Tourette Syndrome

1.1.1 Clinical Features

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the presence of sudden, repetitive, recurrent motor and vocal tics, that can significantly affect the individual's overall health, well-being, and quality of life (Pringsheim et al., 2019). The onset of tics typically occurs during childhood between the ages of 4 and 6, with tic severity reaching its peak between 10 and 12 years of age. While only a small percentage (around 20%) of individuals with TS experience persistent severe symptoms throughout adulthood, the overall prevalence of TS is estimated below 1% in children and 0.1% in adults (Groth et al., 2017; Levine et al., 2019). Tics are generally divided into simple and complex, with simple tics encompassing brief movements confined to single muscle groups or meaningless sounds or noises (e.g., eye blinking or grunting), while complex tics involve longer-lasting movements engaging multiple muscle groups or vocalizations spanning from single words to sentences, both potentially creating an appearance of purposefulness to external observers (Eapen & Robertson, 2015). Tics are often preceded by a premonitory urge (PMU), an uncomfortable and often distressing sensation or feeling of wanting to move. The PMU is often described to build up prior to the onset of the tic, and the subsequent execution of the tic typically provides temporary relief from this sensation (Cavanna et al., 2017). Moreover, advance warning of the occurrence of the tic by the PMU allows the individual to exert conscious cognitive and/or physical effort to prevent or prolong its onset (Ganos et al., 2018). Some individuals might engage in muscle tensing, shifting body positions, or redirecting the PMU into alternative movements. Additionally, individuals might employ cognitive strategies, such as focusing attention away from the urge or engaging in mental tasks to distract from the impending tic. However, tic suppression might be experienced as uncomfortable and stressful and can result in increase of the PMU (Brandt et al., 2016; Ueda et al., 2021). Although tics are generally considered to be involuntary, the phenomena of the PMU and tic suppression argue that tics are rather semi-voluntary responses to the urge (Rae et al., 2019). Importantly, TS is a highly heterogenous disorder, with type, severity, frequency, complexity of tics, as well as the manifestation of PMU and ability to suppress tics, greatly varying from individual to individual, but also within individuals over time (Efron & Dale, 2018). This heterogeneity is unsurprising, given that tics can be influenced by several internal and external factors. For

instance, anxiety, stress, and tiredness have been shown to exacerbate tics, whereas the opposite has been shown for focused attention, task engagement, physical exercise, and relaxation (Iverson & Black, 2022). Moreover, the presence and severity of comorbid conditions contribute to the heterogeneity of the disorder. TS frequently coexists with various psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, mood disorders, and other disruptive behaviors, with approximately 85% of individuals with TS encountering at least one comorbid condition (Hirschtritt et al., 2015). Comorbidities often have an even greater impact on quality of life than the tics themselves (Gill & Kompoliti, 2020).

1.1.2 Pathophysiology of TS

TS has been associated with dysfunctional cortico-basal ganglia-thalamo-cortical circuits (CBGTC), encompassing the cortex, basal ganglia (BG), and thalamus (Mink, 2003). The BG encompass various nuclei, including the striatum (caudate and putamen), subthalamic nucleus (STN), globus pallidus internus and externus (GPi and GPe, respectively), and substantia nigra pars compacta and pars reticulata (SNc and SNr, respectively). Different parts of these structures are connected to different regions in the thalamus and cortex, forming discrete parallel circuits that serve distinct purposes, including sensorimotor, associative, and limbic functions (DeLong & Wichmann, 2010; Krack et al., 2010; Figure 1). Information within these circuits is processed via three different pathways. The direct pathway inhibits the GPi/SNr via the striatum, reducing the inhibitory BG output to the thalamus, and enabling thalamic projections to widespread cortical regions. In contrast, via the indirect pathway, the GPe is inhibited by the striatum, resulting in disinhibition of the STN and enabling the excitation of GPi/SNr through the STN, which in turn increases the inhibitory output of the BG to the thalamus, inhibiting thalamic output to the cortex. Importantly, the output of the striatum strongly depends on excitatory input from the cortex and thalamus, as well as dopaminergic input from the SNc. Lastly, the hyperdirect pathway activates the STN through direct input from the cortex, leading to fast thalamic inhibition (DeLong & Wichmann, 2009; Mink, 2003).

In TS, dysfunctions within the sensorimotor circuit – connecting the putamen (the motor portion of the striatum) to the sensorimotor cortex – are thought to primarily contribute to the initiation and execution of tics (Ganos et al., 2013; Mink, 2003).

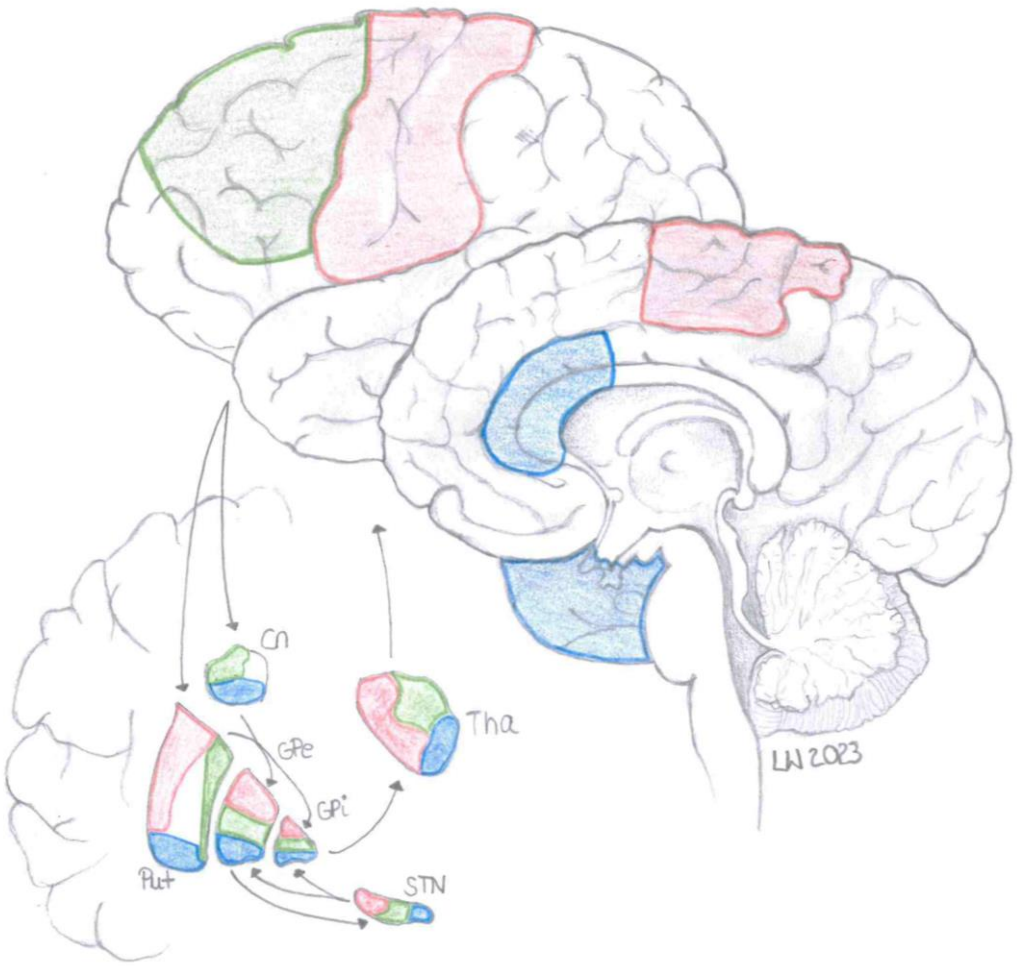

Figure 1: Pseudo-anatomical illustration of the CBGTC circuits. Color-coded regions represent the associative (**red**), sensorimotor (**green**), and limbic (**blue**) circuits. Cortical regions project to the striatum (Cn = Caudate nucleus; Put = Putamen). The direct pathway inhibits the Globus pallidus internus (GPi), disinhibiting the thalamus (Tha) for cortical excitation. The indirect pathway inhibits the Globus pallidus externus (GPe), disinhibiting the Subthalamic nucleus (STN), which activates the GPi, leading to thalamic inhibition. Figure drawn by Laura Wehmeyer (2023), modified from Krack et al., 2010.

In particular, Albin and Mink (2006) proposed that aberrant activity of striatal neurons leads to inappropriate inhibition of GPi/SNr via the direct pathway, thereby reducing the inhibitory BG output to the thalamus, which, in turn, enables the execution of undesired motor behaviors (i.e. tics). Unexpected activation of striatal neurons might be driven by abnormal dopamine neurotransmission consistent with the observed clinical utility of dopamine antagonists in reducing tics (Huys et al., 2012; Maia & Conceição, 2018), impaired GABAergic striatal microcircuitry (Kataoka et al., 2010), and/or abnormal glutamatergic excitatory input from the cortex (Rae et al., 2019). Beyond that, growing evidence indicates that the limbic and

associative CBGTC circuits also play a role in TS (Ganos et al., 2013; Leckman et al., 2010; Wichmann & Delong, 2006). This makes intuitive sense considering the heterogeneous nature of the disorder, encompassing tics, PMU, and ability for tic suppression, alongside the expression of psychiatric comorbidities. Expanding on this, functional magnetic resonance imaging (fMRI) studies have identified a wide network involved in the tic generation, which includes the supplementary motor area (SMA), premotor cortex, insula, sensorimotor cortex, putamen, globus pallidus, and thalamus (Bohlhalter et al., 2006; Neuner et al., 2014; Wang et al., 2011). Notably, cortical activity in the SMA has been observed to precede BG activity during tic generation, implying that dysfunction within the sensorimotor CBGTC circuit could be driven by cortical activity (Ganos et al., 2013; Neuner et al., 2014; Rae et al., 2019). In addition, the primary and secondary sensory cortices, the insula, the anterior cingulate cortex (ACC) and the SMA are thought to contribute to the PMU (Cavanna et al., 2017). In the context of voluntary tic suppression, studies indicate the participation of sensorimotor cortices, the inferior frontal cortex, and the ACC (Ganos, Kahl, et al., 2014; Serrien et al., 2005; van der Salm et al., 2018).

1.1.3 Cognitive Processes in TS

While the hallmark of TS lies in its motor and vocal tics, these primary manifestations are often accompanied by cognitive alterations that can offer valuable insights into the clinical characteristics and underlying pathophysiology of TS (Cavanna et al., 2020). For instance, the phenomenology of tics, particularly their presumed involuntary nature, and the underlying CBGTC dysfunctions, have led to the hypothesis that impaired inhibitory control might contribute to the emergence of tics (Morand-Beaulieu et al., 2017). Over the past decades, this perspective has generated considerable interest in exploring potential volitional cognitive control impairments in TS. Various volitional control tasks, including the Stroop task, the flanker task, Go/ No-Go tasks, the stop-signal task, and task switching task, have been utilized to study both proactive cognitive control – preparing cognitive resources for anticipated demands – and reactive cognitive control – adapting to unexpected challenges or conflicting stimuli (Rawji et al., 2020). However, the evidence regarding volitional cognitive control deficits in patients with TS remains inconclusive. While some studies have indeed reported cognitive performance deficits, others have failed to detect differences between patients with TS and controls, and in some cases, even showed enhanced cognitive control in TS (Morand-Beaulieu et al., 2017). Various factors including sample size, task selection, and participant

characteristics like age, presence of comorbidities, medication use, could potentially account for the divergent findings across studies.

In recent years, there has been growing interest in the phenomenon of premonitory urges preceding the occurrence of tics (Kwak et al., 2003). Exploring the interplay between sensory inputs and subsequent motor responses might offer a promising avenue for understanding the triggers and mechanisms underlying tic manifestation. In this regard, contrary to the prevailing notion of insufficient inhibitory control in TS, an alternative perspective proposes that tics might be semi-voluntary actions triggered by the PMU (Beste & Münchau, 2018; A. Kleimaker et al., 2020). According to this view, tics could arise from heightened habit formation due to an aberrantly strong relationship between perceptual processes (i.e. PMU) and motor actions (i.e. tics), a phenomenon known as perception-action binding (Beste & Münchau, 2018). The underlying neural mechanism could be associated with disrupted striatal processes in TS, given the critical role of the BG in integrating sensory processes for action selection via cortical connections (Beste & Münchau, 2018). Drawing from the theory of event coding (TEC) framework (Hommel, 2009; Hommel et al., 2001), studies have indeed demonstrated altered perception-action binding among TS patients (M. Kleimaker et al., 2020; Mielke et al., 2021; Petruo et al., 2016).

1.1.3.1. Investigating Cognitive Processes using the Task Switching Paradigm

The cued task switching paradigm provides a way to investigate both cognitive control and perception-action binding in TS. This paradigm requires participants to dynamically switch between different task sets – that is different stimulus-response rules. During each trial, participants encounter one of three possible cues: 'COLOR,' 'SHAPE,' or 'NUMBER,' signifying the dimension of the upcoming target stimulus they should focus on, thereby activating the current task set. The target, consisting of one or three symbols shaped as a star or a circle and colored red or yellow, requires a specific response based on the cue (Wehmeyer at al., 2021; for an example see Figure 2).

Figure 2: Example of a target with three stars, requiring a left key response when the cue is 'COLOR' or a right key response when the cue is 'SHAPE' or 'NUMBER'." Adapted from Wehmeyer et al. (2023).

When the cue changes on the next trial (i.e. the task switches), costs usually arise, manifesting as slower and less accurate performance (Monsell, 2003). Two cognitive processes contribute to these switch costs. The first is an endogenous proactive control process, involved in the reconfiguration of the next task set before the target appears (Jamadar et al., 2015; Monsell, 2003; Rogers & Monsell, 1995). Although sufficient time for proactive control can diminish switch costs, residual switch costs persist (Monsell, 2003). Residual switch costs have been ascribed to interference originating from the previous task set after target onset, activating a second exogenous reactive control process involved in resolving this interference (Jamadar et al., 2015; Monsell, 2003; Rogers & Monsell, 1995). Associative binding theories propose that this interference might stem from bindings between task features of the preceding trial (Abrahamse et al., 2016; Frings et al., 2020). All trial features, such as task set, target, and response, are presumed to be stored in a shared event file, which can be reactivated through repetition of any feature in the subsequent trial (Allport & Wylie, 2000; Hommel et al., 2001; Koch et al., 2018; Waszak et al., 2003). Consequently, interference contributing to residual switch costs could originate from task set-target bindings where non-task relevant target features trigger reactivation of the preceding task set (Kopp et al., 2020). Moreover, as a result of reactivation of the preceding event file, bindings between task set and response – task set-response bindings – might also lead to interference for repeated responses on task switch trials and switched responses on task repeat trials (Altmann, 2011; Koch et al., 2018).

In this regard, the cued task switching paradigm offers a controlled and systematic approach to explore cognitive control (i.e. proactive control), perceptual binding (i.e. task set-target bindings), and perception-action binding (i.e. task set-response bindings) processes in TS. By effectively integrating the study of these different cognitive processes, this paradigm not only fosters a comprehensive understanding of the cognitive foundations of TS but also bridges experimental design with the dynamic challenges of real-world cognition.

1.1.4 Treatment of TS

Conventional treatment options for TS include various possible behavioral and pharmacological treatments. Behavioral therapies play a pivotal role in the treatment of individuals with TS, with specific emphasis on Cognitive Behavioral Intervention for Tics (CBIT) and Habit Reversal Training (HRT) (Andren et al., 2022). Both therapies are grounded in the concept that tics are learned behaviors reinforced through operant conditioning (Azrin & Nunn, 1973). The core aim of CBIT and HRT is to equip individuals with TS with skills and

techniques to understand and manage their tics, enhancing daily functioning and overall quality of life. CBIT and HRT share fundamental components, including awareness training and competing response training. Awareness training fosters the recognition of tic onset and awareness of the premonitory urge that precedes tics, which is crucial for initiating effective strategies. Building upon this, competing response training teaches individuals alternative movements or behaviors that counteract tics, performed when premonitory urges arise (Andren et al., 2022). While both therapies share common elements, CBIT provides a more tailored and comprehensive approach for individuals with TS and includes additional components like social support and education, or relaxation training (Wilhelm et al., 2012). The choice between CBIT and HRT depends on an individual's needs, tic severity, and preferences, guided by healthcare professionals. Both therapies have demonstrated effectiveness in assisting individuals with TS in managing tics and enhancing their quality of life (Piacentini et al., 2010; Wilhelm et al., 2012).

While behavioral therapy approaches are recommended as first-line treatment, pharmacological treatments may be considered with caution when tics markedly interfere with everyday life and social interactions, cause subjective discomfort, or result in personal distress (Roessner et al., 2011). Medications primarily targeting dopamine receptors play a central role in TS treatment by modulating dopaminergic neurotransmission (Huys et al., 2012). Antagonistic dopamine receptor drugs, particularly first-generation antidopaminergic medications (typical antipsychotics) like haloperidol and pimozide, are known for their efficacy against tics. However, they often come with notable side effects, including extrapyramidal symptoms, sedation, and weight gain. Second-generation antidopaminergic medications (atypical antipsychotics) like risperidone and aripiprazole offer a more favorable side effect profile, making them more favorable over typical antipsychotics. They are commonly used in TS, particularly for TS patients with comorbid OCD symptoms (Cavanna, 2022; Roessner et al., 2022). Furthermore, benzamides like tiapride, also acting as a selective dopamine antagonist, but with low antipsychotic action, represent an alternative pharmacological treatment with a more tolerable side effect profile and comparable effectiveness (Mogwitz et al., 2018). Other medications used in TS treatment include noradrenergic agents such as clonidine, which are frequently used in children and in cases with comorbid ADHD (Waldon et al., 2013). In recent years, there has been increasing interest among patients with TS in the use of cannabis for self-medication (Milosev et al., 2019). Indeed, research supports a potential role of cannabis-based medicines in the treatment of patients with TS (Müller-Vahl et al., 2023; Thaler et al., 2019).

A small proportion of patients with TS do not respond to conventional treatments or experience intolerable side effect. For these cases of treatment-refractory TS, deep brain stimulation represents a promising treatment option (Johnson et al., 2023).

1.2 Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a minimally invasive neurosurgical procedure that has attracted considerable attention due to its potential to alleviate symptoms associated with range of neurological and psychiatric conditions (Lee et al., 2019). This advanced technique involves the stereotactic implantation of electrodes within specific subcortical brain regions, followed by the delivery of controlled electrical impulses through these electrodes. The electrodes are connected to a neurostimulator, also referred to as implanted pulse generator (IPG), typically placed beneath the collarbone or in the abdomen (Figure 3A). The IPG delivers electrical impulses based on programmed stimulation parameters, including the frequency, pulse width, amplitude (voltage or current), which are continuously adaptable to optimize clinical outcomes while minimizing side effects. Furthermore, electrode contacts can be adjusted for precise targeting, aiming to maximize treatment efficacy with minimal stimulation (Montgomery Jr & Montgomery, 2016). DBS is generally considered safe, although adverse events, such as infections, hardware- or stimulation-related issues may occur (Buhmann et al., 2017). Surpassing its predecessor, the thalamotomy, DBS clearly excels in precision, adaptability, reversibility, and fewer side effects (Benabid et al., 1987). Despite its profound impact, the exact mechanisms of DBS remain unclear. Traditional views of DBS either stimulating or inhibiting the target area have shifted toward a more network-oriented perspective, suggesting that DBS acts through multimodal mechanisms that affect a widespread brain network and go beyond local effects (Ashkan et al., 2017).

Since its first approval for essential tremor (ET) and tremor resulting from Parkinson's disease (PD) in the late 1990 (Miocinovic et al., 2013), DBS has become an established treatment option for movement disorders such as PD, ET, and dystonia (Krack et al., 2019). This success also motivated the application of DBS for non-movement disorders, such as epilepsy, chronic pain, and consciousness disorders, as well as neuropsychiatric disorders, including depression, OCD, TS, substance abuse disorders, eating disorders, and Alzheimer's disease (Lee et al., 2019; Vanhoecke & Hariz, 2017). However, the efficacy of DBS varies by disorder and depends on factors including the targeted brain region, underlying pathology, and patient characteristics.

Apart from its therapeutic utility, DBS offers the unique opportunity to record neural activity from the targeted brain region. Specifically, electrodes used for DBS can also be used to record Local Field Potentials (LFPs) from surrounding neural tissue of the target area. These LFP recordings are traditionally obtained intraoperatively (between the first surgery for lead implantation and the second for IPG implantation) by externalizing DBS electrodes (Figure 3B). However, recordings conducted at this stage may not represent either the pre-surgery or post-surgery state. This discrepancy arises due to the transient 'stun effect,' a phenomenon wherein the local trauma resulting from electrode insertion often impacts both symptoms and neural activity in the targeted brain region (Chen et al., 2006). One way to avoid the stun effect is to record LFPs during the IPG replacement surgery, which is performed every few years unless the neurostimulator can be externally charged (Swan et al., 2014). In addition, LFPs can also be recorded postoperatively if a neurostimulator with brain sensing capabilities has been implanted, such as the first-generation Activa PC + S and second-generation Percept™ PC devices by Medtronic (Cummins et al., 2021) (Figure 3C). These novel sensing devices are integrated alongside the implanted DBS electrodes and are equipped to capture real-time LFPs from the target area at any time after surgery (Neumann et al., 2019). LFP recordings enable the study of neural oscillations deep within the brain. This might contribute to a deeper understanding of neurophysiological mechanisms underlying neurological and neuropsychiatric disorders. In addition, LFP recordings shed light on the mechanisms underlying the therapeutic effects of DBS. The potential of LFP research is exemplified by illuminating discoveries in PD research. Decades of LFP studies in the STN of PD patients unveiled exaggerated beta-frequency (13-30 Hz) oscillations associated with motor symptoms, such as bradykinesia and rigidity (Brown, 2007). Interestingly, high-frequency DBS has been shown to disrupt pathological beta oscillations in the STN, which was associated with improvements in motor symptoms (Eusebio et al., 2011).

1.2.1 DBS for TS

DBS has emerged as a highly promising treatment avenue for patients with treatment-refractory TS. It is important to note that while the US Food and Drug Administration (FDA) and regulatory agencies in other countries have not yet granted formal approval for DBS as a treatment for TS, the ongoing research and promising results underscore its great potential in terms of efficacy and safety (Martinez-Ramirez et al., 2018).

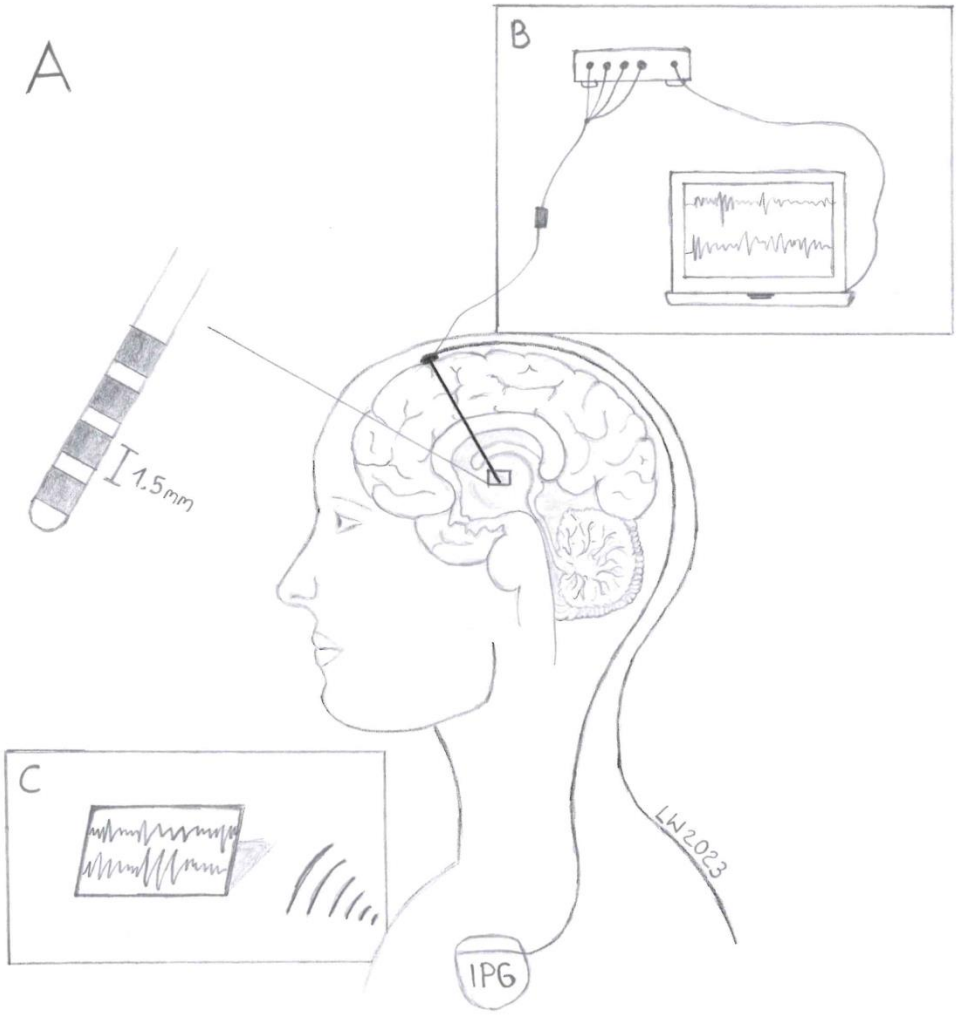

Figure 3: Simplified visualization of a DBS system. **A**) The implanted electrode within deep brain structures with the four exemplary stimulation contacts is connected to the implanted pulse generator (IPG) via an extension cable. **B**) Intraoperatively, LFPs can be recorded from the implanted electrodes by connecting the externalized extension cables to an amplifier and a recording computer before implanting the IPG. **C**) Postoperatively, LFPs can be recorded using an IPG with telemetric brain sensing capabilities. Figure drawn by Laura Wehmeyer (2023).

The first case of DBS in TS was targeted in the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus complex (CM-Spv-Voi) based on insights of earlier thalamic stereotactic lesion studies (Vandewalle et al. 1999; Hassler & Dieckmann, 1970). The choice of target has evolved over time, informed by the involvement of CBGTC circuitry in TS pathophysiology. The thalamus, particularly the centromedian nucleus–nucleus ventrooralis internus (CM-Voi) and centromedian nucleus–parafascicular (CM-Pf) complexes, and the GPi, including anteromedial (amGPi) and posteroventrolateral (pvlGPi) subregions,

have emerged as prominent DBS targets for patients with TS (Heiden et al., 2021). Encouraging outcomes have been observed across these different targets (Baldermann et al., 2016). However, optimal DBS target selection in TS remains controversial due to unclear differences in clinical effects and underlying mechanisms of action among targets. The disorder's heterogeneity further complicates target selection, underscoring the necessity to tailor target selection to individual clinical symptoms and characteristics (Porta et al., 2009). To date, DBS target selection in TS lacks a well-defined rationale, often relying on the preferences and experience of the surgical center (Deeb & Malaty, 2020). All of this emphasizes the ongoing experimental nature of DBS in TS. Therefore, there is a critical need to systematically investigate and compare the clinical effects and outcomes of DBS across different target areas to determine if there are significant differences in their efficacy.

1.2.2 Future Directions for DBS

The field of DBS is rapidly evolving and advancing. As previously mentioned, insights from DBS applications in movement disorders are being extended to a broader range of neuropsychiatric conditions. This is accompanied by a paradigm shift toward personalized and symptom-specific targeting approaches (Horn & Fox, 2020; Krauss et al., 2021). One of the most intriguing advancements in DBS technology is the concept of closed-loop DBS, also referred to as adaptive DBS (Neumann et al., 2023). In contrast to conventional DBS, in which electrical pulses are delivered continuously based on pre-determined parameters, the closed-loop concept entails dynamic adjustment of stimulation parameters in response to real-time neural feedback. In particular, real-time LFPs in the target area are captured by a sensing-enabled implanted neurostimulator, empowering the closed-loop system to activate stimulation or adjust stimulation parameters based on identified pathological activity patterns in the target area (Parastarfeizabadi & Kouzani, 2017).

The concept of closed-loop DBS represents a significant step toward personalized medicine. By continuously monitoring neural dynamics and adapting stimulation in real-time, such a system holds the potential to offer treatments tailored to the patient's immediate needs. This adaptability holds the potential to mitigate side effects and enhance therapeutic outcomes. Furthermore, it could optimize battery usage by administering stimulation selectively when needed (Parastarfeizabadi & Kouzani, 2017). Currently, closed-loop DBS is primarily being explored within the context of PD, where heightened beta band activity serves as a biomarker and feedback signal for adaptive stimulation (Bouthour et al., 2019). However, the practical

implementation of closed-loop DBS remains an area of ongoing research and development. Current challenges encompass finding a reliable biomarker, refining the algorithms governing stimulation adjustments, ensuring reliable sensing, and addressing potential technical issues (Krauss et al., 2021; Parastarfeizabadi & Kouzani, 2017).

Within the context of TS, a closed-loop DBS system seems ideal for the treatment of tics given their paroxysmal nature, characterized by their occurrence in sudden and brief episodes (Andrade & Visser-Vandewalle, 2016). Importantly, the development of a feedback-controlled closed-loop DBS system for TS necessitates the identification of a biomarker, which requires a comprehensive understanding of the underlying pathophysiological mechanisms of the TS symptomatology that could be potentially targeted by stimulation-based interventions.

1.3 Electrophysiology

1.3.1 Electrophysiological Approaches for Uncovering TS Pathophysiology

Electrophysiology offers a particularly well-suited approach for investigating the underlying pathophysiological mechanisms of TS and identifying potential markers linked to TS symptoms. These techniques, which measure electrical currents and voltage changes within the brain, serve as powerful tools for studying temporal brain dynamics. For instance, electroencephalography (EEG) capturing cortical activity from the scalp, and LFPs obtained from implanted DBS electrodes, directly measure real-time brain electrical activity (Cohen, 2014). While electrophysiological techniques, such as EEG, may have limited spatial resolution compared to fMRI, they stand out for their high temporal resolution in the order of milliseconds (He & Liu, 2008). The real-time capability is essential for monitoring immediate fluctuations in brain activity linked to TS symptoms and for analyzing rapid cognitive processes, neural timing, and inter-regional information exchanges within neural networks. This is crucial for developing a future closed-loop DBS system for TS. Specifically, examining non-oscillatory event-related potentials (ERPs), such as the P3 and N2 components that reflect cognitive processes, as well as oscillatory activity across delta (1-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (13-30 Hz) and gamma (>30 Hz) frequency bands, whether time-locked or not, can provide crucial insights into abnormal neural activity patterns (Cohen, 2014; Luck, 2005). Hence, the application of electrophysiological techniques in TS research contributes to understanding underlying neuropathological mechanisms and has the potential to identify electrophysiological markers.

1.3.2 Previous Investigations of Electrophysiological Correlates of TS

Previous electrophysiological studies in TS particularly aimed to establish links between specific neural patterns and cognitive processes. This was motivated by the hypothesis that impaired volitional cognitive control processes may underlie the primary symptom manifestation in TS, namely tics. Consequently, extensive research has addressed the neural underpinnings of cognitive control in TS by analyzing ERPs in volitional control tasks (Morand-Beaulieu & Lavoie, 2019). ERPs, which are averaged brain activity time-locked to a stimulus or response, encompass various well-studied components distinguished by their polarity (positive or negative) and the specific time window in which they occur. These components capture real-time activity patterns associated with specific stages of information processing, with early ERP components corresponding to perceptual, later components to motor, and intermediate components to cognitive processes (Luck, 2005). ERP components can be elicited through multiple cognitive tasks, but the nature and timing of particular ERP components might differ based on the task being performed. A comprehensive meta-analysis by Morand-Beaulieu and Lavoie (2019) synthesized findings from the various volitional control tasks used to study ERPs in TS. Among the key cognitive ERP components scrutinized, the fronto-central N2 and parietal P3, also commonly referred to as P3b, have emerged as focal points of investigation. The fronto-central N2 is widely recognized for its association with cognitive control processes, specifically related to conflict resolution and response inhibition (Folstein & Van Petten, 2008). The parietal P3 is a well-documented reflection of working memory processes, involved in stimulus discrimination and evaluation, context updating, and response selection (Polich, 2007). Nevertheless, very mixed findings have been observed across studies comparing these components between individuals with TS and healthy controls (Morand-Beaulieu & Lavoie, 2019). Notably, several factors, including task variability, comorbid conditions, and symptom severity, likely contribute to large discrepancies across studies. Furthermore, it has been proposed that conventional ERP components, such as the N2 and P3b, may not be ideally suited for capturing processes linking perception and response (Verleger et al., 2014; Wolff et al., 2017). Latencies of such stimulus-response linking processes tend to exhibit greater variability across trials compared to, for example, stimulus-locked perceptual processes or response-locked motor processes. Non-locked processes with high trial-to-trial latency variability are unlikely to be captured by the averaged ERP across trials (Ouyang et al., 2011). This concern becomes particularly relevant when dealing with uncontrolled heightened intra-individual latency variability within one of the comparison

groups, a scenario that might be of particular significance for individuals with TS (Petruo et al., 2019).

Moreover, driven by the emerging perspective of tics being linked to heightened perception-action binding, research has begun to explore the neural underpinnings of these binding processes in TS. Importantly, studies have demonstrated that the most effective approach for investigating electrophysiological correlates of perception-action binding involves overcoming the limitations of conventional averaged ERPs by isolating these processes through temporal EEG signal decomposition (Opitz et al., 2020; Takacs et al., 2020). This can be achieved through the application of residue iteration decomposition (RIDE), which separates single-trial ERPs into distinct clusters: a stimulus-locked S-cluster, a response-locked R-cluster, and a non-locked central C-cluster (Ouyang et al., 2011). The resulting clustered data can then be subjected to similar component analysis methods as traditional ERPs. Interestingly, applying this technique, a recent study by M. Kleimaker et al. (2020) showed altered modulations of the parietal P3 C-cluster component underlying perception-action binding processes in patients with TS. This observation underscores the importance of investigating the interplay between perceptual processes and motor actions in TS.

Collectively, previous investigations into the electrophysiological correlates of TS, with a specific focus on altered cognitive processes that may contribute to tic occurrence, have yielded inconclusive results. This underscores the need for a comprehensive electrophysiological investigation that encompasses the multifaceted cognitive dimensions of TS. In light of this, the cued task switching paradigm, in conjunction with techniques like RIDE, provides a controlled and systematic approach to integrate the study of different cognitive processes, including proactive control, perceptual binding, and perception-action binding, all within a single experimental design. This integration is invaluable for a comprehensive understanding of the complex cognitive foundations of TS and their neurophysiological correlates, and promises to provide deeper insights into the mechanisms underlying TS symptoms.

1.4 Objectives

The pathophysiology of TS remains incompletely understood. While tics represent the hallmark of TS, the presence of co-occurring cognitive symptoms may contribute to their occurrence. However, evidence concerning impaired volitional cognitive control in TS remains inconclusive, with recent research pointing to the role of heightened perception-action binding in TS pathophysiology (Beste & Münchau, 2018; M. Kleimaker et al., 2020; Morand-Beaulieu et al., 2017; Morand-Beaulieu & Lavoie, 2019). To address this knowledge gap, the first objective of this dissertation is to conduct a comprehensive electrophysiological investigation of cognitive processes that may contribute to the occurrence of tics. This investigation employs the task-switching paradigm in conjunction with RIDE, thereby integrating various cognitive processes, including volitional cognitive control and binding, to provide a holistic understanding of the complex cognitive foundations of TS and their neurophysiological correlates (Wehmeyer et al., 2023).

Moreover, ongoing research yields promising results regarding the effectiveness and safety of DBS in patients with treatment-refractory TS (Martinez-Ramirez et al., 2018). However, the selection of DBS targets for TS remains controversial due to unclear distinctions in clinical effects and underlying mechanisms of action (Deeb & Malaty, 2020). To address this issue, the secondary objective of this dissertation is to evaluate the efficacy of DBS in TS and systematically compare target-specific clinical effects through a systematic review and meta-analysis, following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; Page et al., 2021; Wehmeyer et al., 2021). This analysis is vital for understanding the potential mechanisms underlying DBS and guiding future research directions to advance the knowledge of DBS as a treatment approach for TS.

Through this multidimensional approach, this dissertation seeks to deepen our understanding of TS pathophysiology and DBS applications. The resulting prospects for DBS in TS are discussed in detail, with particular attention to potential future closed-loop DBS systems. As a result, this research represents a first step toward paving the way for more personalized stimulation-based treatment strategies, such as closed-loop DBS, with the ultimate goal of enhancing the quality of life for individuals with TS.

2. Empirical Section

2.1 Study 1: Electrophysiological Correlates of Proactive Control and Binding Processes during Task Switching in Tourette Syndrome

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Wehmeyer, L., Schüller, C. B., Gruendler, T. O., Huys, D., Kuhn, J., Ullsperger, M., ... & Schüller, T. (2023). Electrophysiological correlates of proactive control and binding processes during task switching in Tourette syndrome. *Eneuro*, *10*(4). Doi: 10.1523/ENEURO.0279-22.2023

Electrophysiological correlates of proactive control and binding processes during task switching in Tourette syndrome

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Abbreviated title: Task switching in Tourette syndrome

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Author contributions: L.W., C.B.S., T.O.J.G., D.H., J.K., M.U., V.V.-V., P.A., J.C.B., and T.S. designed research; L.W., C.B.S., and T.S. performed research; L.W. and T.S. analyzed data; L.W. and T.S. wrote the paper.

Acknowledgements: This study was supported by the Marga und Walter Boll Stiftung (210-06-16) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) (SFB 1451, Project-ID 431549029). This work was also supported by the Article Processing Charge from the DFG (491454339).

Abstract

The occurrence of tics in Tourette syndrome (TS) has often been linked to impaired cognitive control, but empirical findings are still inconclusive. A recent view proposes that tics may be the result of an abnormally strong interrelation between perceptual processes and motor actions, commonly referred to as perception-action binding. The general aim of the present study was to examine proactive control and binding effects in the context of task switching in adult human patients with TS and matched healthy controls. A cued task switching paradigm was employed in 24 patients (18 male, 6 female) and 25 controls while recording electroencephalography (EEG). Residue iteration decomposition (RIDE) was applied to analyze cue-locked proactive cognitive control and target-locked binding processes. Behavioral task switching performance was unaltered in patients with TS. A cue-locked parietal switch positivity, reflecting proactive control processes involved in the reconfiguration of the new task did not differ between groups. Importantly, target-locked fronto-central (N2) and parietal (P3) modulations, reflecting binding processes between perception and action, differed between groups. Underlying neurophysiological processes were best depicted after temporal decomposition of the EEG signal. The present results argue for unaltered proactive control but altered perception-action binding processes in the context of task switching, supporting the view that the integration of perception and action is processed differently in patients TS. Future studies should further investigate the specific conditions under which binding may be altered in TS and the influence of top-down processes, such as proactive control, on bindings.

Key words: EEG; perception-action binding; proactive control; RIDE; task switching; Tourette syndrome

Significance Statement

The origin of tics in Tourette syndrome is still poorly understood. Based on the phenomenon of the premonitory urge, it has recently been proposed that tics may be the result of an abnormally strong interrelation between perceptual processes and motor actions, i.e. increased perception-action binding. In the present study, we investigated binding effects in the context of a task switching paradigm using EEG to determine underlying neurophysiological mechanisms. Our results suggest that fronto-central (N2) and parietal (P3) activity are

differentially modulated by binding between perception and action in patients with Tourette syndrome, supporting the view that the integration of perception and action is processed differently and may relate to the core symptoms of the disorder, urges and tics.

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics, which are usually preceded by a premonitory urge (PMU) that ceases after tic execution (Brandt et al., 2016). Tics can be voluntarily suppressed for a limited period of time (Ganos et al., 2018). While the pathophysiology of TS is still incompletely understood, symptoms are assumed to be related to dysfunctions of cortico-basal ganglia-thalamo-cortical circuits with altered dopaminergic neurotransmission playing a central role (Albin and Mink, 2006; Maia and Conceição, 2018; Rae et al., 2019). The phenomenology of tics has led to the assumption that cognitive control processes might be impaired in patients with TS, but empirical findings are inconclusive (Ganos et al., 2014; Morand-Beaulieu et al., 2017). Recently, TS symptoms have been linked to an abnormally strong interrelation between perceptual processes (i.e. PMU) and motor actions (i.e. tics), commonly referred to as perception-action binding (Beste and Münchau, 2018).

Both cognitive control and perception-action binding can be investigated with the cued task switching paradigm. Here, a cue signals which task should be performed (e.g., attend to the shape of the target stimulus) to select the appropriate response (e.g., pressing the right button to select the star as shown in **Figure 1**). When the cue signals a switch of tasks, costs can be observed in the form of longer reaction times and higher error rates (Monsell, 2003). Cognitive processes contributing to switch costs can be dissociated on a neurophysiological level (Jamadar et al., 2015). Proactive control processes involved in the reconfiguration of the new task set (i.e. mental representation of the task) have been associated with a sustained parietal modulation after cue onset termed ‘switch positivity’ (Nicholson et al., 2005; Travers and West, 2008; Karayanidis and Jamadar, 2014). Of note, recent behavioral studies have shown that proactive control is likely not impaired in TS (Rawji et al., 2020; Indrajeet et al., 2022). Given sufficient time to execute proactive control, switch costs can be diminished, but residual switch costs still remain (Monsell, 2003). Residual switch costs have been attributed to interference from previous trials, which in turn is associated with target-locked frontal (N2) and parietal (P3) modulations (Allport and Wylie, 2000; Karayanidis and Jamadar, 2014; Kopp et al., 2020). Associative binding theories suggest that interference may arise from bindings

between task features from the previous trial (Abrahamse et al., 2016; Frings et al., 2020). All features of the current trial including task set (activated by the cue), target and response are assumed to be stored in a common event file that may be reactivated by repetition of any feature in the following trial (Allport and Wylie, 2000; Hommel et al., 2001; Waszak et al., 2003; Koch et al., 2018). In particular, bindings between task set and target (task set-target bindings) may cause task-irrelevant target features to trigger reactivation of the previous task set (Kopp et al., 2020). Additionally, bindings between task set and response (task set-response bindings) may cause interference for switched responses on task repeat trials and repeated responses on task switch trials due to reactivation of the previous event file (Altmann, 2011; Koch et al., 2018). Recent studies particularly point to stronger associations between stimulus and response in TS, hence increased perception-action binding (Petruo et al., 2016; Kleimaker et al., 2020). Therefore, in patients with TS task set-response binding may be also altered in the context of task switching.

To date, task switching processes and corresponding electrophysiological modulations have not been investigated in TS. Therefore, our objective was to examine proactive control and binding processes in adult patients with TS and matched healthy controls using a cued task switching paradigm. Importantly, electrophysiological correlates of binding are best depicted when disentangled from pure stimulus or response processes using residue iteration decomposition (RIDE). RIDE separates the event-related potential (ERP) into a stimulus-locked S-cluster, response-locked R-cluster and intermediate C-cluster (Ouyang et al., 2011). Binding as well as task switching processes have been shown to be particularly well reflected by the C-cluster in the N2/P3 time window at both parietal and frontal electrode sites (Wolff et al., 2017; Kleimaker et al., 2020; Opitz et al., 2020).

We hypothesized unaltered behavioral task switch costs and increased task set-response binding effects in patients with TS. Furthermore, we expected a parietal switch positivity before target onset and task set-response binding modulations of frontal/parietal activity in the N2/P3 time window. We assume that these electrophysiological modulations are specific to the C-cluster rather than the S-/R-cluster or non-decomposed ERP. Finally, electrophysiological modulations were examined for group differences.

Materials and Methods

Participants

Twenty-five adult patients with TS were recruited at the University Hospital Cologne, and 25 healthy participants matched for gender, age and years of education were gathered through public advertisements (for demographic data see **Table 1**). One patient was excluded due to an excessive error rate (59 %). Each participant was clinically assessed using standardized clinical assessments. Tic severity was scored using the clinician-rated Yale Global Tic Severity Scale (YGTSS; (Leckman et al., 1989). Additional self-report scales were administered to screen for secondary and comorbid symptoms. Specifically, the PMU was measured using the Premonitory Urge for Tics Scale (PUTS; (Woods et al., 2005). Obsessive-compulsive disorder (OCD) symptoms were tested with the revised Obsessive-Compulsive Inventory (OCI-R; (Foa et al., 2002) and symptoms of depression were rated with the Beck Depression Inventory - Version II (BDI–II; (Beck et al., 1996). Retrospective symptoms of attention-deficit hyperactivity disorder (ADHD) during childhood were scored on the Wender Utah Rating Scale (WURS-K; (Retz-Junginger et al., 2002) (for group comparison results see **Table 1**).

Table 1: Demographic data and results of group comparisons.

	TS	HC	*t*	*df*	*p*
Age	30.21 (9.07)	29.40 (9.28)	0.308	47	0.759
Sex (M/F)	18/6	17/8	0.294[1]	1	0.754
Years of education	11.75 (1.22)	12.12 (1.17)	-1.083	47	0.284
BDI-II	12.13 (9.27)	5.28 (5.19)	3.207	47	0.002 *
OCI-R	20.52 (12.27)	10.92 (7.58)	3.309	47	0.002 *
WURS-K	26.54 (11.64)	16.04 (9.55)	3.458	47	0.001 *
YGTSS total	27.63 (11.47)				
YGTSS global	53.88 (20.49)				
PUTS	30.27 (4.12)				

Data are mean (SD). TS = Tourette patients; HC = Control participants; BDI-II = Beck Depression Inventory II; OCI-R = Obsessive-compulsive Inventory Revised; WURS- K = Wender Utah Rating Scale; YGTSS = Yale Global Tic Severity Scale; PUTS = Premonitory Urge for Tics Scale. Asterisk denotes statistical significance. [1] Chi-square.

Of the 24 included patients, six were taking prescribed medication for the management of their tics at the time of testing. A total of five patients were treated with neuroleptics (3 x aripiprazole, 1 x tiapride, 1 x risperidone) and one with tetrabenazine. These patients were asked to stop medication 24 hours before the testing. All participants had normal or corrected-to-normal vision. Each participant provided oral and written informed consent. The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne (No. 16-491) and performed in accordance with the Declaration of Helsinki.

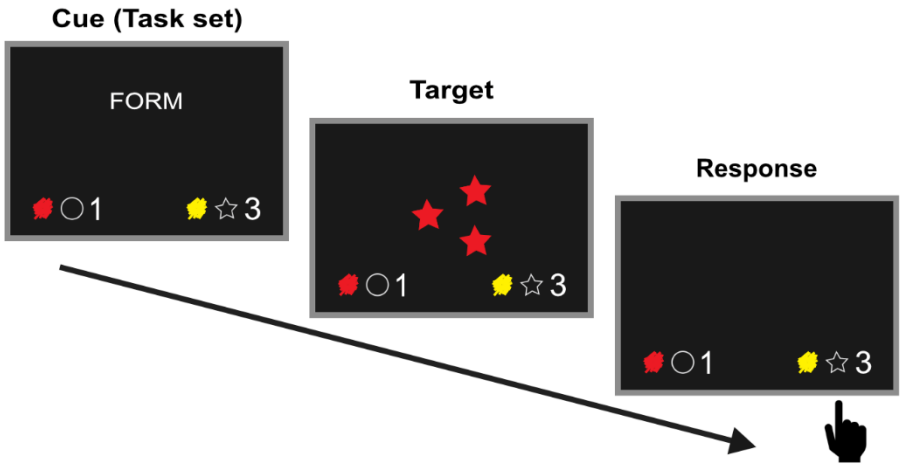

Figure 1: Illustration of one trial of the task switching paradigm. The cue signals which task should be performed (i.e. attend to the shape of the target stimulus), thereby activating the corresponding task set. The target stimulus then requires pressing the right key for star according to the assignment of the target features to the left or right response key in the lower corners. The timing of the stimuli is described in the text.

Experimental Design

Participants performed a computer-based cued task switching paradigm (**Figure 1**) which was administered using Presentation 16.3 (Neurobehavioral Systems, Inc., Berkeley, CA, USA). Responses were given via a response pad (RB-840, Cedrus, San Pedro, CA, USA). After initial practice trials, the task consisted of 432 trials. Each trial began with the presentation of one of three possible cues in German ('FARBE', 'FORM' or 'ANZAHL' corresponding to 'COLOR', 'SHAPE' or 'NUMBER') representing the task according to which the following target stimulus had to be classified. The cue was depicted for either 100 ms (short cue-target interval (CTI)) or 400 ms with a subsequent waiting interval of 400 ms (long CTI) until the target stimulus was presented for 300 ms followed by a blank screen. The target consisted of either one or three symbols, shaped as a star or circle, and colored either red or yellow. Each target feature was assigned to a left or right response key (i.e. 'RED', 'CIRCLE', and '1' = left key; 'YELLOW', 'STAR'; or '3' = right key). The assignment of the features to the keys remained

the same throughout the paradigm and was always displayed in the lower corners of the screen. Participants had to focus on the target feature indicated by the cue and respond as quickly as possible by pressing the appropriate key. Responses had to be executed within 1800 ms after target onset. Once the response was made or after 1800 ms, a blank screen was presented for the response-cue interval (RCI) that randomly varied between 1000, 1500 and 2000 ms before the next trial started. The number of task repeat (cue indicating the same relevant dimension as in the trial before) and task switch (cue indicating a different relevant dimension) trials was counterbalanced in a pseudo-randomized order. The task comprised of four blocks separated by short pauses, the length of which was determined by the participants.

EEG Recording and Analyses

EEG was recorded from 63 Ag/AgCl (EASYCAP GmbH, Herrsching, Germany) electrodes according to the extended 10–20 system. Recordings were performed with a sampling rate of 5000 Hz and all impedances were kept below 15 kΩ. Data was pre-processed and analyzed offline using EEGLAB 2022.1 (Delorme and Makeig, 2004) and custom Matlab R2021b routines (The Mathworks, Natick, MA, USA). The data were filtered using a finite impulse response filter with cut-off frequencies of 0.5 and 40 Hz (6 dB/Octave) and resampled to 500 Hz. Abnormal channels with a low correlation with neighboring channels (channel criterion = 0.8) were removed (removed channels: TS: 1.21 ± 2.11 SD, Controls: 1.64 ± 1.73 SD) and interpolated using spherical splines (Perrin et al., 1989). Between-block rest periods and redundant data before and after the task were also removed. Then, EEG data were re-referenced to an average reference and the FCz reference channel was added back. For the identification of artifacts, an extended infomax independent component analysis (ICA) was run on the continuous data. Resulting independent components were then submitted to the fully automated artifact classifier MARA (Winkler et al., 2011). A total of 18.75 ± 7.01 (SD) independent components remained for the TS group and 25.00 ± 9.07 (SD) for the control group. Next, cue-locked epochs were created from 500 ms before to 3000 ms after cue onset and baseline-corrected by removing the mean voltage calculated over the time window of 200 ms before cue onset. For each participant, the first trial in each block was removed. Additionally, only correct trials that also followed a correct trial with a CTI of 800 ms and with reaction times (RTs) below 1800 ms were considered for further analysis steps.

For the cue-locked analysis, sub-epochs from 200 ms before to 1000 ms after cue onset were extracted and divided into separate segments for each Task Transition condition (i.e. task repeat, task switch). An automated artifact rejection based on extreme values and improbability

was applied to the segmented data (Delorme et al., 2007). Epochs were rejected if amplitudes reached a threshold of ± 150 μV or the joint data probability exceeded 5 standard deviations (average rejected epochs per condition: TS: 3.25 ± 1.64 SD, Controls: 3.44 ± 1.38 SD). Further, current source density (CSD) transformation was performed using the potential difference between one electrode and the potential total of all surrounding electrodes (Kayser and Tenke, 2006). To perform traditional ERP analyses, trials were averaged for each condition and subject, and mean amplitudes were extracted for the switch positivity at left lateral parieto-occipital electrodes (P5/PO3/PO7) over a time window of 400 to 800 ms after cue onset. The choice of electrodes was confirmed by a validation method in which the differential mean activity (task switch – task repeat) of each electrode was compared to that of all other electrodes using false discovery rate (FDR) for multiple comparison correction (adjusted threshold of $p <$ .0007).

For the target-locked analysis, target-locked epochs from -200 ms to 2100 ms (the upper epoch limit ensures that the epoch time window covers up to 300 ms after the latest possible response) were generated. Separate segments were created for each Task Transition/Response Transition condition (i.e. task repeat and response repeat, task repeat and response switch, task switch and response repeat, task switch and response switch). Following the same procedure as for the cue-locked analysis, artifactual epochs were rejected (average rejected epochs per condition: TS: 1.16 ± .84 SD, Controls: 1.28 ± 1.16 SD) and CSD transformation was applied. After averaging the ERP over trials for each condition and subject, mean amplitudes were calculated within a time window of 200 to 500 ms after target onset. Fronto-central electrode Cz was selected for the N2 component and left lateral parieto-occipital electrodes (P5/PO3/PO7) for the P3 component. Similar to the cue-locked analysis, the choice of electrodes was confirmed by the same validation method, but this time using mean amplitudes.

In a next step, the segmented single-trial data were temporally decomposed using the RIDE toolbox (for further details see http://cns.hkbu.edu.hk/RIDE.htm) (Ouyang et al., 2015a, b). For the cue-locked data, RIDE clusters were derived from a prespecified time window from 0 to 600 ms after cue onset for the S-cluster and from 200 to 800 ms for the C-cluster. For the target-locked data, the following RIDE clusters were extracted: S-cluster from 0 to 600 ms after target onset, the C-cluster from 150 to 1000 ms, and the R-cluster from -300 to 300 ms around the response. To quantify the mean amplitudes in each of the obtained RIDE clusters, we focused on the same time windows and electrodes as described above for the cue- and target-locked ERP analyses. Also, the same validation methods were used to confirm electrode sites and time windows for the C-cluster.

Statistical Analysis

Statistical analyses were performed with SPSS 29 (IBM Corp., New York, NY, USA). For analyses of the behavioral data, repeated-measures ANOVAs with 'Group' (patients, controls) as between-subject factor and 'Task Transition' (repeated vs switched task) and 'Response Transition' (repeated vs switched response) as within-subject factors were performed for RTs and error rates. In correspondence with the EEG analyses, only correct trials that also followed a correct trial, with a CTI of 800 ms and with RTs below 1800 ms were included. The first trial in each block was excluded. For analyses of the neurophysiological data, mean amplitudes of each RIDE cluster and the standard ERP were analyzed using repeated-measures ANOVAs with 'Group' as between-subject factor and 'Task Transition' and 'Response Transition' as within-subject factors. However, the latter within-subject factor was only included for the target-locked analysis. Significant ANOVA effects were followed up with Bonferroni-corrected post-hoc pairwise comparisons. In addition, a repeated-measures ANCOVA with 'Medication' (non-medicated vs medicated) as covariate was performed in order to control for medication as a confounding factor. Effect sizes are reported as partial eta-squared ($\eta\rho^2$). The Bayesian posterior probability of the null hypothesis being true given the observed data ($p_{BIC}(H_0|D)$) is reported when of theoretical importance. In doing so, we followed the method proposed by Masson (2011) based on Wagenmakers (2007), which generates Bayesian probabilities using the Bayesian information criterion (BIC) estimate of the Bayes factor derived from ANOVA sum of squares. Obtained probabilities are interpreted according to the classification scheme of Raftery (1995) (i.e. .50-.75 = weak evidence; .75-.95 = positive evidence; .95-.99 = strong evidence; > .99 = very strong evidence). In an exploratory analysis, Spearman's correlations were calculated to test the relationship between behavioral and neurophysiological effects and clinical parameters (YGTSS total tic, PUTS, BDI-II, OCI-R, WURS-K) for the TS group only.

Results

Behavior

The RTs and error rates of each group are shown in **Figure 2**. For RTs, there was a significant main effect of Task Transition ($F_{(1,47)} = 45.71$, $p < 0.001$, $\eta\rho^2 = 0.493$) with slower RTs on task switch than task repeat trials, which might indicate proactive control and/or task set-target binding processes. No main effects of Response Transition ($F_{(1,47)} = 2.63$, $p = 0.111$, $\eta\rho^2 = 0.053$) or Group ($F_{(1,47)} = 1.30$, $p = 0.260$, $\eta\rho^2 = 0.027$) were observed. The interactions between

Task Transition x Group ($F_{(1,47)}$ = 0.77, p = 0.386, ηρ² = 0.016) and Response Transition x group ($F_{(1,47)}$ = 1.02, p = 0.318, ηρ² = 0.021) were also non-significant. Importantly, task set-response binding processes would be indicated by an interaction between Task Transition and Response Transition. However, both interaction effects between Task Transition x Response Transition ($F_{(1,47)}$ = 0.02, p = 0.896, ηρ² = 0.000, $p_{BIC}(H_0|D)$ = 0.874) and Task Transition x Response Transition x Group ($F_{(1,47)}$ = 0.12, p = 0.735, ηρ² = 0.002, $p_{BIC}(H_0|D)$ = 0.868) were non-significant, with Bayesian analyses providing positive evidence for the null hypotheses. After including medication as a covariate, the Task Transition main effect remained significant ($F_{(1,46)}$ = 32.43, p < 0.001, ηρ² = 0.413). The analysis of error rates revealed a significant main effect of Task Transition ($F_{(1,47)}$ = 53.33, p < 0.001, ηρ² = 0.532), suggesting that error rates increased for task switch trials. Again, no main effect of Response Transition ($F_{(1,47)}$ = 1.48, p = 0.229, ηρ² = 0.031) or Group ($F_{(1,47)}$ = 1.90, p = 0.174, ηρ² = 0.039) was found, and no interactions between Task Transition x Group ($F_{(1,47)}$ = 1.93, p = 0.171, ηρ² = 0.040) and Response Transition x group ($F_{(1,47)}$ = 0.93, p = 0.341, ηρ² = 0.019). Similarly, the interactions between Task Transition x Response Transition ($F_{(1,47)}$ = 2.85, p = 0.098, ηρ² = 0.057) and Task Transition x Response Transition x Group ($F_{(1,47)}$ = 0.17, p = 0.685, ηρ² = 0.004) were not significant. However, Bayesian analyses provided only weak evidence for the null hypothesis of the former ($p_{BIC}(H_0|D)$ = 0.624), but positive evidence for the latter ($p_{BIC}(H_0|D)$ = 0.865). When controlling for medication, the Task Transition main effect remained significant ($F_{(1,46)}$ = 43.39, p < 0.001, ηρ² = 0.485).

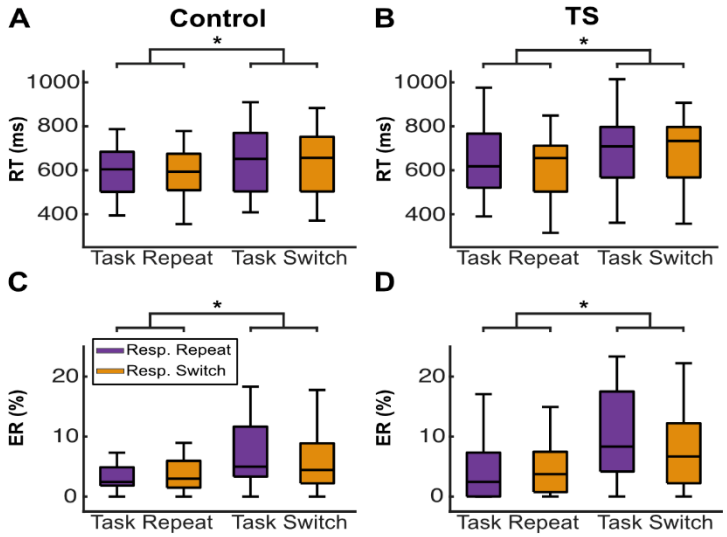

Figure 2: Behavioral results. Boxplots for reaction times (RT) and error rates (ER) separately for controls and patients. ***A***, RTs for controls. ***B***, RTs for patients. ***C***, ERs for controls. ***D***, ERs for patients. Asterisks denote significant differences between experimental conditions.

Neurophysiology

Cue-locked parietal switch positivity:

In the C-cluster, cue-locked parietal activity was significantly modulated by Task Transition ($F_{(1,47)}$ = 31.12, p < 0.001, ηρ² = 0.398), corresponding to an increased positivity for task switch trials (**Figure 3**). The Group main effect ($F_{(1,47)}$ = 0.00, p = 0.998, ηρ² = 0.000) and Task Transition x Group interaction effect ($F_{(1,47)}$ = 0.00, p = 0.948, ηρ² = 0.000) were non-significant. Bayesian analysis provided positive evidence for a similar effect of Task Transition in both groups ($p_{BIC}(H_0|D)$ = 0.875). The Task Transition main effect was not modified by medication ($F_{(1,46)}$ = 26.23, p < 0.001, ηρ² = 0.363).

In the S-cluster and conventional ERP, similar effects were observed (**Extended Data Figure 3-1, Extended Data Figure 3-2**).

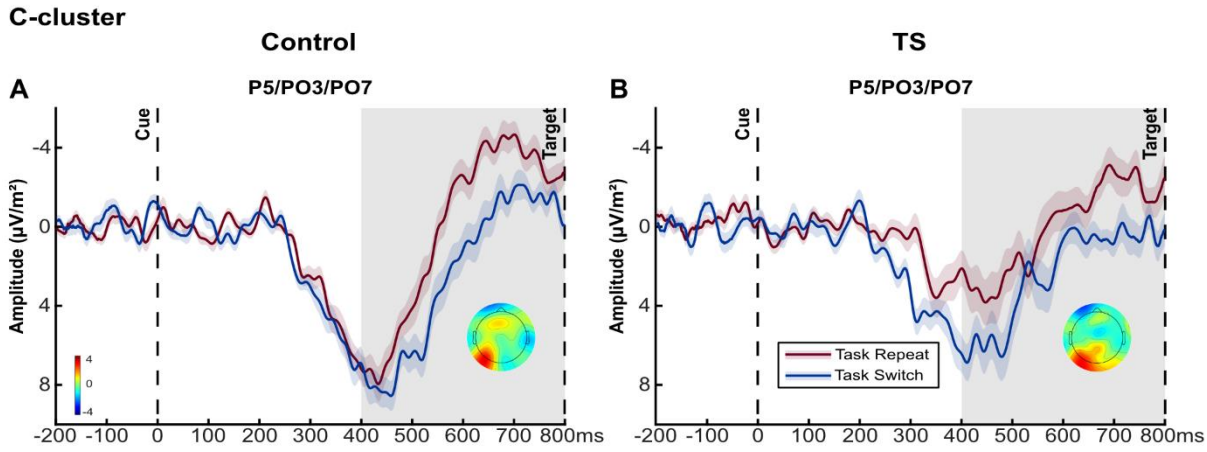

Figure 3: Cue-locked switch positivity results. Grand average cue-locked waveforms at electrodes P5/PO3/PO7 in the C-cluster separately for controls and patients. ***A***, in the control group. ***B***, in the TS group. Shading represents standard error. The grey bar indicates the time window for mean amplitude quantification (400-800 ms). Scalp topography maps show the differences in mean amplitude (task switch - task repeat) in the respective time window. See **Extended Data Figure 3-1** for the ANOVA results in the S-cluster and ERP and **Extended Data Figure 3-2** for the corresponding waveforms.

Target-locked frontal N2:

In the C-cluster, no main effects of Task Transition ($F_{(1,47)}$ = 0.84, p = 0.364, $\eta\rho^2$ = 0.018), Response Transition ($F_{(1,47)}$ = 0.56, p = 0.459, $\eta\rho^2$ = 0.012) or Group ($F_{(1,47)}$ = 1.02, p = 0.317, $\eta\rho^2$ = 0.021) were observed. Similarly, there were no significant two-way interactions (all p > 0.064). However, the three-way interaction between Task Transition x Response Transition x Group was significant ($F_{(1,47)}$ = 9.60, p = 0.003, $\eta\rho^2$ = 0.170). Importantly, this three-way interaction points to differential task set-response binding processes between groups. In the control group, post-hoc pairwise comparisons demonstrated a significantly increased negativity for switched responses compared to repeated responses on task repeat trials (p = 0.004), and a numerically increased negativity for repeated responses compared to switched responses on task switch trials, but this effect was non-significant (p = 0.097) (**Figure 4A,B**). In the TS group, however, none of the post-hoc pairwise contrasts were significant (all p > 0.448) (**Figure 4C,D**). Importantly, the three-way interaction remained significant when controlling for medication ($F_{(1,46)}$ = 10.65, p = 0.002, $\eta\rho^2$ = 0.188).

In the R-cluster, a significant main effect of Response Transition ($F_{(1,47)}$ = 7.72, p = 0.008, $\eta\rho^2$ = 0.141) was observed, indicating an increased positivity for repeated response compared to switched responses. There were no significant main effects of Task Transition ($F_{(1,47)}$ = 0.01, p = 0.935, $\eta\rho^2$ = 0.001) or Group ($F_{(1,47)}$ = 0.02, p = 0.885, $\eta\rho^2$ = 0.000). Also, no significant two-way interactions were found (all p > 0.071). Importantly, similar to the C-cluster, the three-way interaction between Task Transition x Response Transition x Group was significant ($F_{(1,47)}$ = 4.68, p = 0.036, $\eta\rho^2$ = 0.090). In the control group, post-hoc pairwise comparisons demonstrated a significantly increased positivity for repeated responses compared to switched responses on task switch trials (p < 0.001), while Response Transition conditions did not differ on task repeat trials (p = 0.910) (**Figure 4E,F**). In the TS group, none of the post-hoc pairwise contrasts were significant (all p > 0.229) (**Figure 4G,H**). When medication was included as covariate, the effects of Response Transition and Task Transition x Response Transition x Group remained significant ($F_{(1,46)}$ = 4.15, p = 0.047, $\eta\rho^2$ = 0.083; $F_{(1,46)}$ = 4.73, p = 0.035, $\eta\rho^2$ = 0.083, respectively).

In the S-cluster and standard ERP, no significant effects were found after controlling for medication (**Extended Data Figure 4-1, Extended Data Figure 4-2**).

Figure 4: Target-locked N2 results.

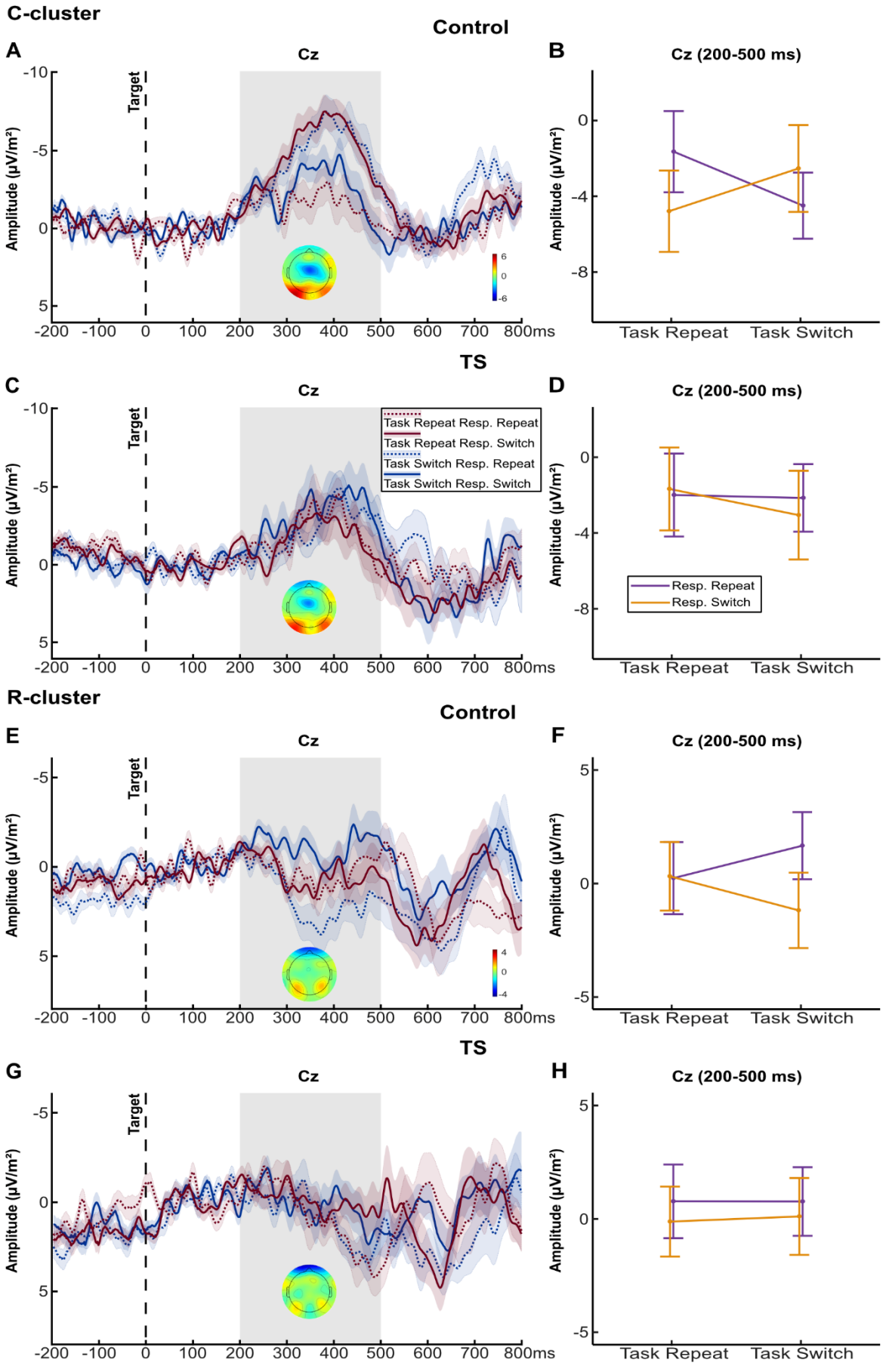

Figure 4: Continued.

Grand average target-locked waveforms at electrode Cz in the C- and R-cluster separately for controls and patients. ***A***, C-cluster waveform at Cz in the control group. ***B***, C-cluster mean amplitudes at Cz in the time interval 200-500 ms in the control group. ***C***, C-cluster waveform in the TS group. ***D***, C-cluster mean amplitudes in the TS group. ***E***, R-cluster waveform in the control group. ***F***, R-cluster mean amplitudes in the control group. ***G***, R-cluster waveform in the TS group. ***H***, R-cluster mean amplitudes in the TS group. Shading and error bars indicate standard errors. The grey bar indicates the time window for mean amplitude quantification (200-500 ms). Scalp topography maps show mean amplitudes in the respective time window. Resp. = Response. See **Extended Data Figure 4-1** for the ANOVA results in the S-cluster and ERP and **Extended Data Figure 4-2** for the corresponding waveforms.

Target-locked parietal P3:

In the C-cluster, there were no significant main effects of Task Transition ($F_{(1,47)}$ = 0.44, p = 0.511, $\eta\rho^2$ = 0.009), Response Transition ($F_{(1,47)}$ = 2.15, p = .645, $\eta\rho^2$ = .058) or Group ($F_{(1,47)}$ = 0.15, p = 0.697, $\eta\rho^2$ = 0.003). Similarly, no significant two-way interactions were found (all p > 0.408). However, a significant three-way interaction between Task Transition x Response Transition x Group was observed ($F_{(1,47)}$ = 7.48, p = 0.009, $\eta\rho^2$ = 0.137), indicating differential task set-response binding processes between groups. In the control group, post-hoc analysis revealed a significantly increased positivity for switched responses compared to repeated responses on task switch trials (p = 0.040), whereas Response Transition conditions did not differ significantly on task repeat trials (p = 0.719) (**Figure 5A,B**). In the TS group, the opposite pattern was observed: a significantly increased positivity for repeated responses compared to switched responses on task switch trials (p = 0.035), whereas the effect of Response Transition on task repeat trials was also not significant (p = 0.222) (**Figure 5C,D**). When accounting for a potentially confounding effect of medication, the three-way interaction remained significant ($F_{(1,46)}$ = 6.40, p = 0.015, $\eta\rho^2$ = 0.122).

In the S-cluster, mean amplitudes of the target-locked parietal P3 were significantly modulated by Task Transition ($F_{(1,47)}$ = 6.68, p = 0.013, $\eta\rho^2$ = 0.124), indicating an increased positivity for task repeat compared to task switch trials (**Figure 5E,F**). The main effects of Response Transition ($F_{(1,47)}$ = 1.08, p = 0.304, $\eta\rho^2$ = 0.023) and Group ($F_{(1,47)}$ = 0.094, p = 0.336, $\eta\rho^2$ = 0.020) were not significant, including the two-way interactions between Task Transition x Group ($F_{(1,47)}$ = 0.12, p = 0.726, $\eta\rho^2$ = 0.003), Response Transition x Group ($F_{(1,47)}$ = 0.66, p = 0.423, $\eta\rho^2$ = 0.014) and Task Transition x Response Transition ($F_{(1,47)}$ = 1.81, p = 0.85, $\eta\rho^2$ = 0.037). Additionally, Bayesian analysis provided positive evidence for a similar

effect of Task Transition in both groups ($p_{BIC}(H_0|D)$ = 0.868). The three-way interaction between Task Transition x Response Transition x Group was also non-significant ($F_{(1,47)}$ = 0.09, p = 0.764, $\eta\rho^2$ = 0.002, $p_{BIC}(H_0|D)$ = 0.870), which was supported by Bayesian analysis yielding positive evidence for the null hypothesis (**Extended Data Figure 5-2A,B**). The main Task Transition effect was not influenced by medication ($F_{(1,46)}$ = 11.66, p = 0.001, $\eta\rho^2$ = 0.202).

While no significant effects were found in the R-cluster, mean amplitudes in the ERP were similarly modulated as in the S-cluster (**Extended Data Figure 5-1, Extended Data Figure 5-2C-F**).

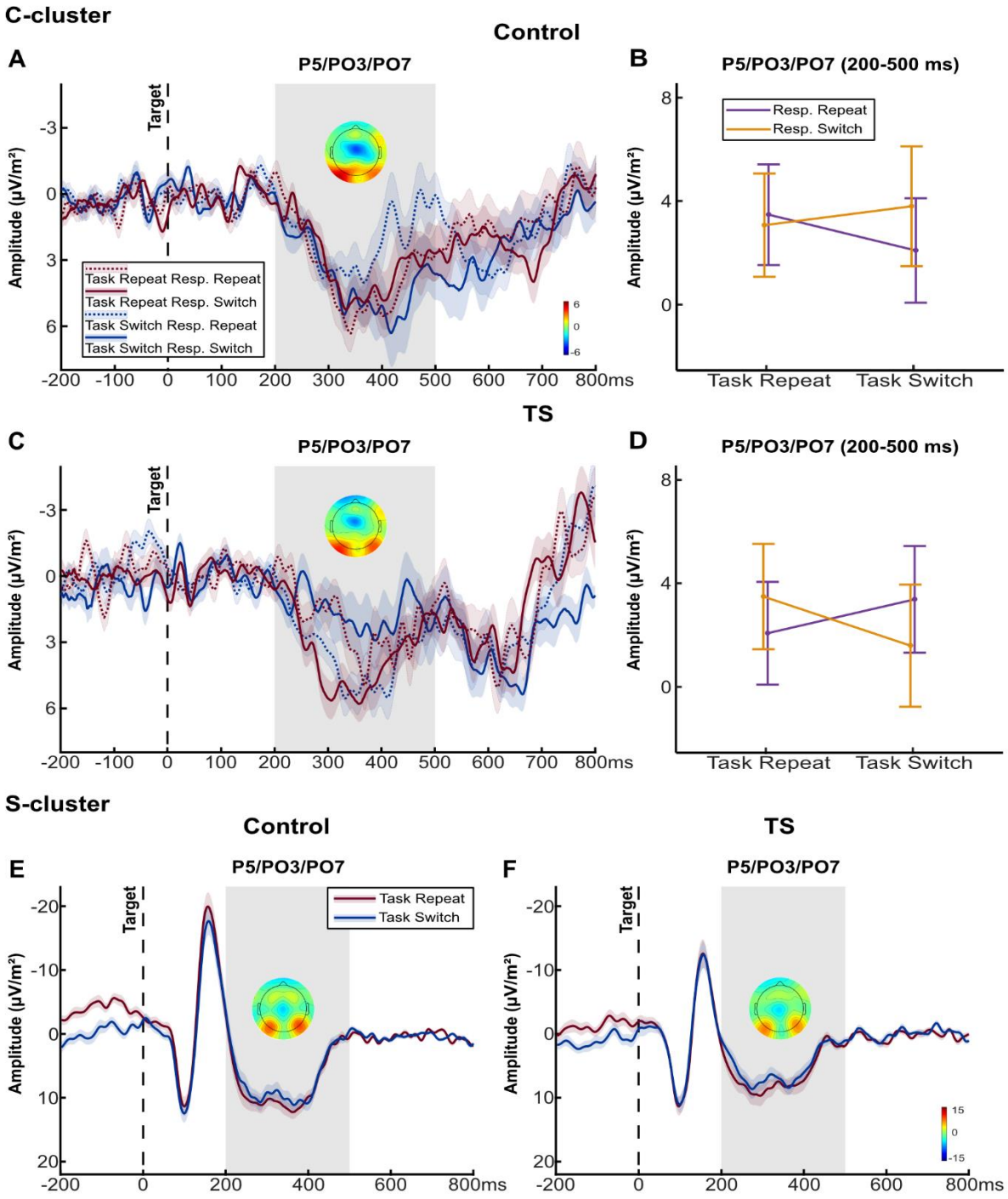

Figure 5: Target-locked P3 results. Grand average target-locked waveforms at electrodes P5/PO3/PO7 in the C- and S-cluster separately for controls and patients. ***A***, C-cluster waveform at P5/PO3/PO7 in the control group. ***B***, C-cluster mean amplitudes at P5/PO3/PO7 in the time interval 200-500 ms in the control group. ***C***, C-cluster waveform in the TS group. ***D***, C-cluster mean amplitudes in the TS group. ***E***, S-cluster waveform in the control group. ***F***, S-cluster waveform in the TS group. Shading and error bars indicate standard errors. The grey bar indicates the time window for mean amplitude quantification (200-500 ms). Scalp topography maps show mean amplitudes in the respective time window. Resp. = Response. See **Extended Data Figure 5-1** for the ANOVA results in the R-cluster and ERP, and **Extended Data Figure 5-2** for the corresponding R-cluster/ERP waveforms, as well as the S-cluster waveform for each experimental condition.

Exploratory correlations

For the behavioral effects, task switch costs (task switch-RT – task repeat-RT, task switch-ER – task repeat-ER) were computed and correlated with clinical scores in the TS group. No significant correlations were observed (all $r < 0.30$; $p > 0.161$; see **Table 2**). For the neurophysiological effects, differential mean activity between conditions corresponding to neurophysiological findings in the TS group (i.e. C-cluster switch positivity: task switch – task repeat, R-cluster N2: response repeat – response switch, C-cluster P3: response repeat – response switch in task switch, S-cluster P3: task repeat – task switch) was quantified and correlated with clinical measurements. We found an uncorrected negative correlation between the parietal S-cluster Task Transition effect and PUTS scores ($r = -0.48$; $p = 0.019$), indicating smaller Task Transition effects with increased PMU severity. No further significant correlations between other neurophysiological effects and clinical scores (all $r < 0.34$; $p > 0.113$) were observed (see **Table 2**).

Table 2: Spearman's correlation coefficients.

		YGTSS total	PUTS	BDI-II	OCI-R	WURS-K
RT Task Transition (task switch – task repeat)	*r*	0.20	-0.08	0.24	-0.14	0.30
	p	0.378	0.700	0.254	0.507	0.161
ER Task Transition (task switch – task repeat)	*r*	-0.04	-0.24	0.15	-0.13	-0.17
	p	0.853	0.260	0.481	0.555	0.427
C-SP Task Transition (task switch – task repeat)	*r*	-0.33	0.24	-0.05	0.06	0.30
	p	0.121	0.265	0.823	0.765	0.157
R-N2 Response Transition (response repeat – response switch)	*r*	0.32	-0.09	0.157	0.166	0.20
	p	0.125	0.669	0.465	0.437	0.361
C-P3 Response Transition (response repeat – response switch) in Task Switch	*r*	-0.14	0.201	-0.11	0.06	-0.17
	p	0.947	0.346	0.466	0.785	0.438
S-P3 Task Transition (task repeat – task switch)	*r*	-0.33	-0.48	-0.02	-0.19	-0.30
	p	0.113	0.019 *	0.938	0.386	0.149

RT = Reaction time; ER = Error rate; C-SP = C-cluster switch positivity; R-N2 = R-cluster N2; C-P3 = C-cluster P3; S-P3 = S-cluster P3; YGTSS = Yale Global Tic Severity Scale; PUTS = Premonitory Urge for Tics Scale; BDI-II = Beck Depression Inventory II; OCI-R = Obsessive-compulsive Inventory Revised; WURS- K = Wender Utah Rating Scale. Asterisk denotes statistical significance.

Discussion

In the present study, we examined cue-locked proactive control and target-locked binding processes during task switching in adult patients with TS and matched healthy controls using residue iteration decomposition (RIDE).

The present results indicate that both groups showed the expected behavioral switch costs (i.e. increased reaction times and error rates on task switch trials), which are generally attributed to proactive control processes for task-set reconfiguration as well as to interference caused by bindings between task set and target features of the previous trial (Monsell, 2003; Abrahamse et al., 2016). As hypothesized, task switch costs did not differ between groups, and no relationship between tic-severity and switch costs was found, likely indicating that proactive control is unaltered in TS in line with former behavioral studies (Morand-Beaulieu et al., 2017; Rawji et al., 2020; Indrajeet et al., 2022). This was further corroborated by our neurophysiological results, where both groups exhibited a similar cue-locked switch positivity, which has been suggested to reflect proactive reconfiguration of the new task set (Kieffaber and Hetrick, 2005; Nicholson et al., 2005; Rushworth et al., 2005; Lavric et al., 2008; Travers and West, 2008; Karayanidis and Jamadar, 2014). Additionally, the comparable behavioral task switch costs between groups indicate unaltered task set-target binding in TS. This is consistent with predictions from perception-action binding accounts, which state that altered binding in TS specifically includes actions (Beste and Münchau, 2018). In support of this, both groups showed similarly modulated activity in the S-cluster that strongly resembles the previously reported task switch P3, which presumedly represents processes necessary to overcome target-driven interference induced by task set-target bindings (Kieffaber and Hetrick, 2005; Karayanidis and Jamadar, 2014; Jamadar et al., 2015). The P3 modulation was most pronounced in the S-cluster, which is thought to primarily reflect stimulus processes, i.e. perception and attention (Ouyang et al., 2011). Interestingly, we found an, albeit exploratory, negative relationship between the S-cluster P3 and PMU severity, indicating a smaller difference between task conditions with increased urge severity. This might indicate disrupted representations of task set-target bindings or diminished activation of processes involved in overcoming task set-target binding-induced interference in patients that experience severe urges, either way suggesting a association between altered perceptual binding processes and PMU.

Generally, task set-response bindings are represented behaviorally by costs (i.e. increased reaction times and error rates) for switched responses on task repeat trials and for repeated

responses on task switch trials (Gade et al., 2014; Koch et al., 2018). Contrary to our expectations, we did not observe such a behavioral effect in either group. This implies that the binding between task set and response, or the retrieval (reactivation) of this binding, was not strong enough to impact behavior (Dutzi and Hommel, 2009; Frings et al., 2020; Hommel, 2022). When comparing our study to others investigating perception-action binding, it is important to keep in mind that our task notably differs from the commonly used visual-motor event file task (Colzato et al., 2006). In particular, we examined bindings between task set and response and not between target and response. Task set-response bindings can be modulated by proactive control processes between cue and target, which is not the case for target-response bindings. It can be speculated that proactive control processes promoting the current goal (i.e. task set) may have influenced the likelihood of binding or retrieval of bindings, which may have contributed to the fact that participants did not show task set-response binding effects on a behavioral level as expected (Dutzi and Hommel, 2009; Hommel, 2022). Nevertheless, our decomposed EEG data provide evidence that target-locked processes in fronto-central (N2) as well as parietal (P3) regions were indeed influenced by task set-response (perception-action) binding.

First, we observed task set-response binding in the C-cluster N2, which is in line with previous findings showing that C-cluster activation reflects perception-action binding particularly well (Kleimaker et al., 2020; Opitz et al., 2020). Importantly, C-cluster N2 modulation related to task set-response binding was observed in the control group only, whereas there was no such modulation in the TS group. Increased N2 amplitudes have been consistently linked to increasing levels of interference and have been suggested to play an important role in conflict resolution and response selection (Karayanidis et al., 2003; Gajewski et al., 2010; Karayanidis and Jamadar, 2014). A recent study also demonstrated that fronto-central C-cluster activity was similarly modulated by distractor-response binding (Opitz et al., 2020). Based on this, we speculate that the C-cluster N2 effect in the control group represents a process of conflict resolution and is thus related to overcoming task set-response binding-induced interference. However, because this modulation is not corroborated by a corresponding behavioral task set-response binding effect, no conclusion can be drawn regarding the behavioral significance of this modulation. Nevertheless, the lack of fronto-central modulation in the TS group suggests binding-induced conflict is processed differently. Of note, R-cluster N2 activity was also modulated by task set-response binding, albeit with a smaller effect size than in the C-cluster. This modulation is unlikely to represent binding processes per se, but may be related to pure motor processes in line with the conceptualized role of R-cluster

activations (Ouyang et al., 2011). Additionally, the parietal C-cluster P3 modulation by task set-response binding also differed between groups. While C-cluster P3 activation decreased for repeated responses on task switch trials in the control group, it increased in the TS group. The observed C-cluster P3 modulations in the control group are in line with findings showing that the task switching N2 and P3 are tightly coupled and increased N2 amplitudes are consistently accompanied by decreased P3 amplitudes (Karayanidis and Jamadar, 2014). Also, decreased C-cluster P3 activation has been repeatedly linked to increased perception-action binding-induced interference when response selection became more difficult and rebinding processes more complex (Petruo et al., 2016; Kleimaker et al., 2020; Takacs et al., 2020). Again, we want to point out that our findings are not corroborated by corresponding behavioral effects and therefore we can only speculate that this modulation is likewise related to binding-induced interference requiring a rebinding. Interestingly, our results show that the C-cluster P3 is oppositely modulated in the TS group, with increased activation in response to binding-induced interference. A recent study investigating perception-action binding in TS reported a similar finding, with parietal C-cluster amplitudes increasing in the less compatible condition (Kleimaker et al., 2020). Although the underlying process behind this modulation in the TS group is currently unclear, our results corroborate that parietal processes related to perception-action binding are altered in patients with TS.

The present findings complement the existing literature by demonstrating that proactive control processes in the context of task switching are not impaired in patients with TS. Rather, our neurophysiological results support the recent view that perception-action binding is altered in TS. Our results highlight that, above all, the interrelation of sensory and motor processes is highly relevant for a better understanding of the complex symptomatology of TS. This especially relates to the relationship between urges and tics, implying that the investigation of solely sensory processes (PMU) or motor actions (tics) are likely insufficient for this purpose.

Several limitations of the present study need to be addressed. First, the sample size is rather small, which limits statistical power. Second, effects of target-response bindings could not be examined in the present study because the trial structure of the paradigm was not counterbalanced to allow for a reliable assessment. Third, five patients were taking neuroleptic medications regularly but paused 24 hours before testing to minimize acute effects. However, an effect of medication cannot be completely ruled out. To account for a potentially confounding effect, we report medication as a covariate. Fourth, patients with TS showed significant elevated scores on depression, ADHD, and OCD questionnaires, which could have influenced our results. However, comorbidity scores did not correlate with task modulations.

Last, we would like to emphasize that neurophysiological correlates of task set-response binding did not have a decisive influence on behavioral performance. Therefore, it is unclear whether the observed neuronal modulations are meaningful for subsequent behavioral adjustments. This needs to be addressed in future studies.

In sum, we examined proactive control and binding processes in the context of task switching in patients with TS and matched healthy controls. Behavioral performance and electrophysiological modulations of proactive control involved in the reconfiguration of the new task were unaltered in TS patients. Importantly, C-cluster N2 and P3 modulations reflecting task set-response binding were altered, supporting the recent view that the integration of perception and action is processed differently in patients TS and may relate to the core symptoms of the disorder, sensory urges and motor tics. Future studies may further investigate the potential influence of different task characteristics and top-down processes such as proactive control on behavioral and neurophysiological binding processes in patients with TS.

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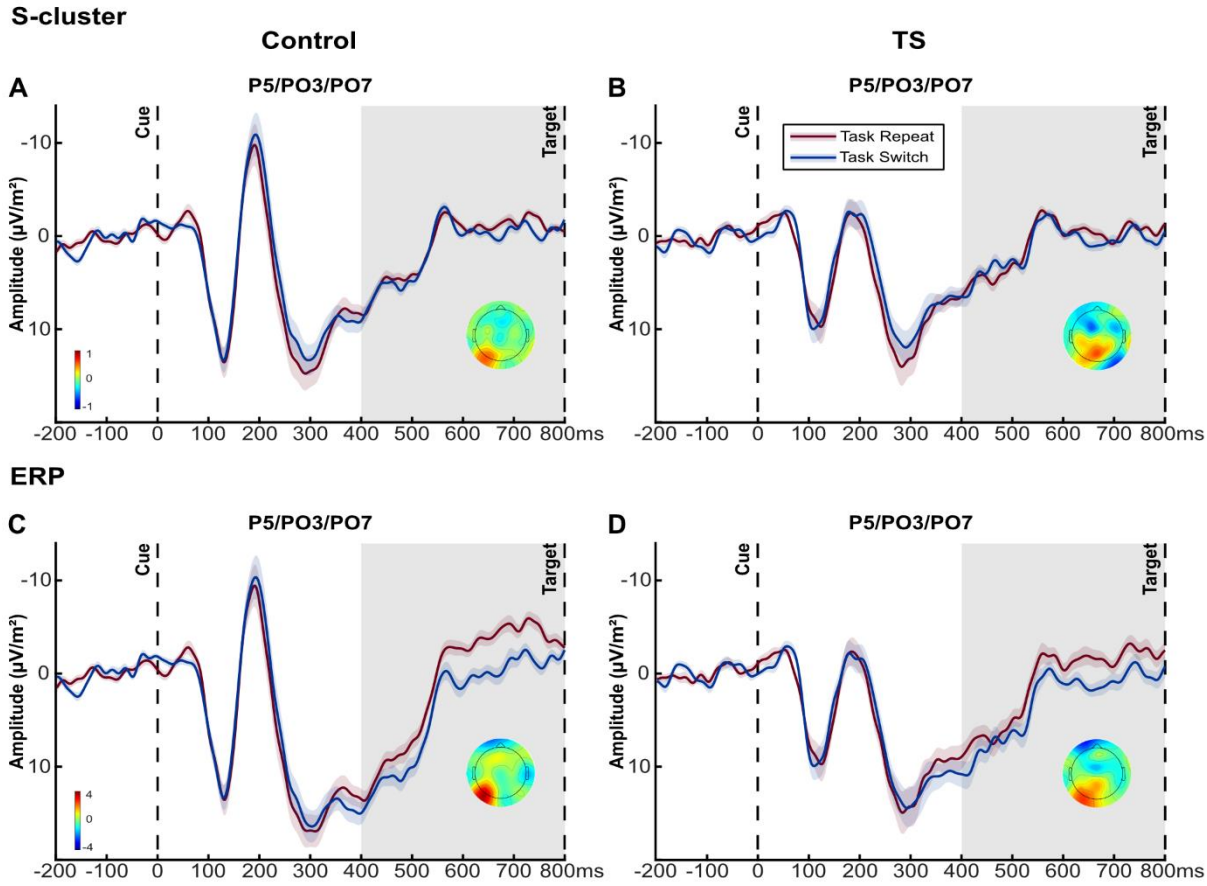
Extended Data

Extended Data Figure 3-1: Cue-locked switch positivity ANOVA results for the S-cluster and ERP.

Switch positivity	ANOVA				ANCOVA			
	$F_{(1,47)}$	p	ηp^2	$P(H_0\|D)$	$F_{(1,46)}$	p	ηp^2	$P(H_0\|D)$
S-cluster								
Task Transition	7.53	0.009*	0.138	0.155	6.87	0.012*	0.130	0.188
Task Transition x Group	0.145	0.705	0.003	0.866				
Group	0.06	0.810	0.001	0.872				
ERP								
Task Transition	31.45	< 0.001*	0.401	0.000	27.46	< 0.001*	0.374	0.000
Task Transition x Group	0.65	.425	0.014	0.834				
Group	0.01	.924	0.000	0.874				

*Significant ANOVA effects were followed up by an ANCOVA with Medication as covariate. Asterisk denotes statistical significance. $P(H_0|D)$ = probability of the null hypothesis being true given the observed data. See **Extended Data Figure 3-2** for the corresponding waveforms.*

Extended Data Figure 3-2: Cue-locked switch positivity results.



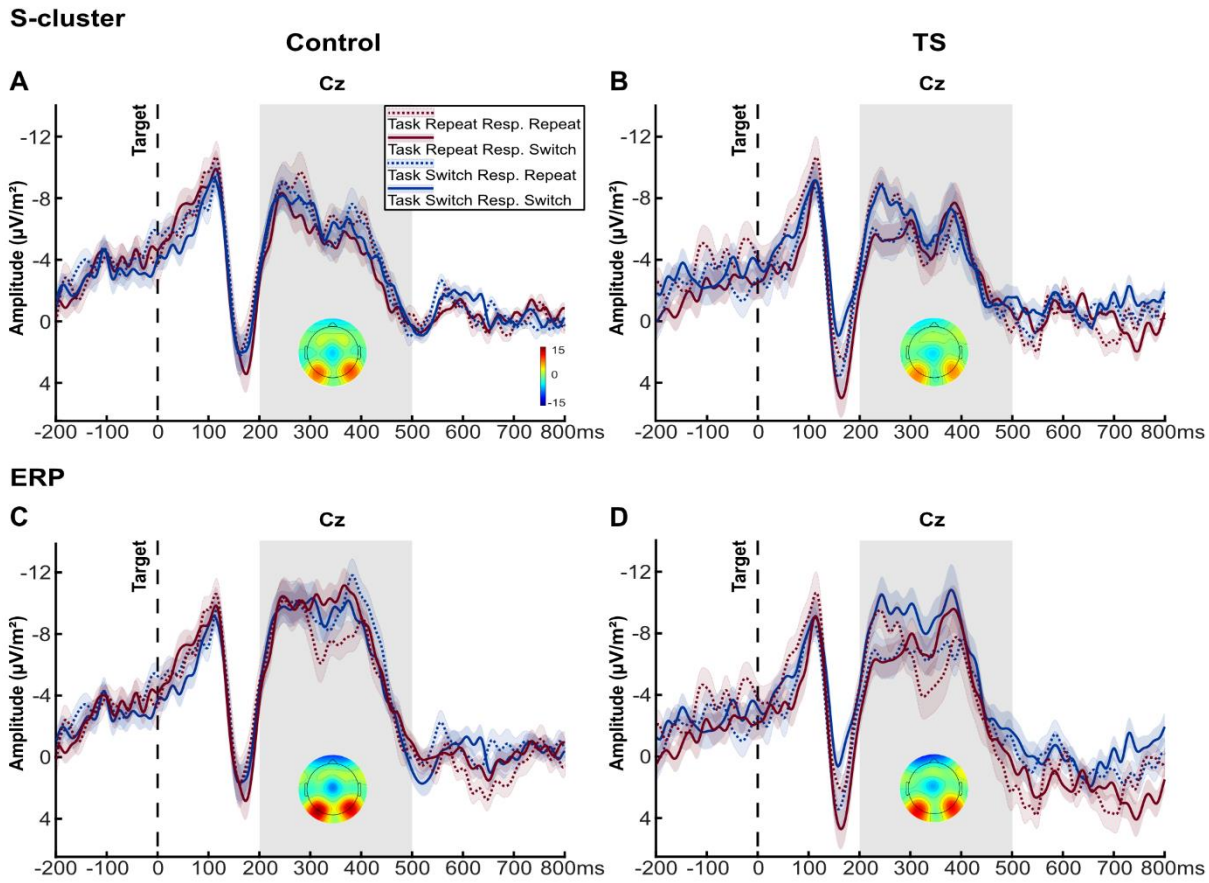
Grand average cue-locked waveforms at electrodes P5/PO3/PO7 in the S-cluster and standard ERP separately for controls and patients. ***A***, S-cluster waveform in the control group. ***B***, S-cluster waveform in the TS group. ***C***, ERP waveform in the control group. ***D***, ERP waveform in the TS group. Shading represents standard error. The grey bar indicates the time window for mean amplitude quantification (400-800 ms). Scalp topography maps show the differences in mean amplitude (task switch - task repeat) in the respective time window. See **Extended Data Figure 3-1** for the corresponding ANOVA results.

Extended Data Figure 4-1: Target-locked N2 ANOVA results for the S-cluster and ERP.

N2	ANOVA				ANCOVA			
	$F_{(1,47)}$	p	ηp^2	$P(H_0\|D)$	$F_{(1,46)}$	p	ηp^2	$P(H_0\|D)$
S-cluster								
Task Transition	0.06	0.801	0.001	0.871				
Response Transition	0.15	0.696	0.003	0.866				
Group	0.26	0.616	0.005	0.860				
Task Transition x Group	0.17	0.682	0.004	0.865				
Response Transition x Group	0.89	0.351	0.019	0.816				
Task Transition x Response Transition	5.07	0.029 *	0.097	0.362	3.99	0.052	0.080	0.477
Task Transition x Response Transition x Group	0.03	0.873	0.001	0.874				
ERP								
Task Transition	2.59	0.114	0.052	0.652				
Response Transition	2.33	0.133	0.047	0.681				
Group	1.31	0.258	0.027	0.781				
Task Transition x Group	0.62	0.434	0.013	0.835				
Response Transition x Group	0.73	0.396	0.015	0.827				
Task Transition x Response Transition	0.00	0.973	0.000	0.875				
Task Transition x Response Transition x Group	3.54	0.066	0.070	0.541				

Significant ANOVA effects were followed up by an ANCOVA with Medication as covariate. Asterisk denotes statistical significance. $P(H_0|D)$ = probability of the null hypothesis being true given the observed data. See ***Extended Data Figure 4-2*** *for the corresponding waveforms.*

Extended Data Figure 4-2: Target-locked N2 results.



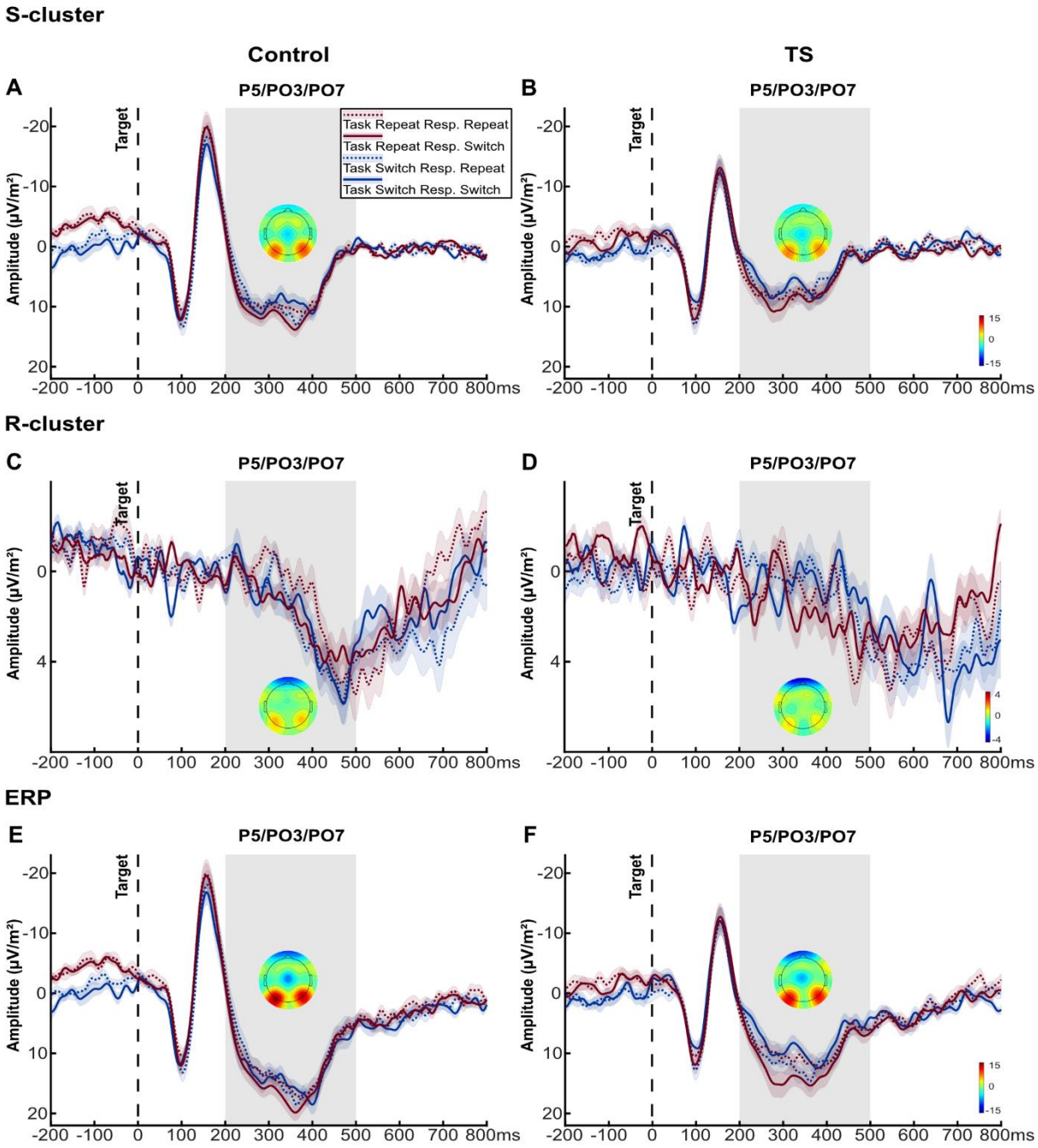
Grand average target-locked waveforms at electrode Cz in the S-cluster and standard ERP separately for controls and patients. ***A***, S-cluster waveform in the control group. ***B***, S-cluster waveform in the TS group. ***C***, ERP waveform in the control group. ***D***, ERP waveform in the TS group. Shading represents standard error. The grey bar indicates the time window for mean amplitude quantification (200-500 ms). Scalp topography maps show mean amplitudes in the respective time window. Resp. = Response. See **Extended Data Figure 4-1** for the corresponding ANOVA results.

Extended Data Figure 5-1: Target-locked P3 ANOVA results for the R-cluster and ERP.

P3	ANOVA				ANCOVA			
	$F_{(1,47)}$	p	ηp^2	$P(H_0\|D)$	$F_{(1,46)}$	p	ηp^2	$P(H_0\|D)$
R-cluster								
Task Transition	0.32	0.573	0.007	0.856				
Response Transition	1.12	0.295	0.023	0.797				
Group	1.71	0.198	0.035	0.745				
Task Transition x Group	3.66	0.062	0.072	0.527				
Response Transition x Group	0.01	0.925	0.000	0.874				
Task Transition x Response Transition	0.436	0.512	0.009	0.848				
Task Transition x Response Transition x Group	0.032	0.860	0.001	0.873				
ERP								
Task Transition	6.28	0.016 *	0.118	0.245	8.59	0.005 *	0.157	0.095
Response Transition	2.92	0.094	0.058	0.615				
Group	1.24	0.272	0.026	0.788				
Task Transition x Group	1.27	0.265	0.026	0.784				
Response Transition x Group	2.02	0.162	0.041	0.714				
Task Transition x Response Transition	2.79	0.101	0.056	0.630				
Task Transition x Response Transition x Group	2.47	0.123	0.050	0.666				

Significant ANOVA effects were followed up by an ANCOVA with Medication as covariate. Asterisk denotes statistical significance. $P(H_0|D)$ = probability of the null hypothesis being true given the observed data. See ***Extended Data Figure 5-2*** *for the corresponding waveforms.*

Extended Data Figure 5-2: Target-locked P3 results.



Grand average target-locked waveforms at electrodes P5/PO3/PO7 in the S-cluster, R-cluster, and standard ERP separately for controls and patients. ***A***, S-cluster waveform in the control group. ***B***, S-cluster waveform in the TS group. ***C***, R-cluster waveform in the control group. ***D***, R-cluster waveform in the TS group. ***E***, ERP waveform in the control group. ***F***, ERP waveform in the TS group. Shading represents standard error. The grey bar indicates the time window for mean amplitude quantification (200-500 ms). Scalp topography maps show mean amplitudes in the respective time window. Resp. = Response. See **Extended Data Figure 5-1** for the corresponding ANOVA results for the R-cluster and ERP.

2.2 Study 2: Target-Specific Effects of Deep Brain Stimulation for Tourette Syndrome: A Systematic Review and Meta-Analysis

The following chapter is reproduced from the original publication:

Wehmeyer, L., Schüller, T., Kiess, J., Heiden, P., Visser-Vandewalle, V., Baldermann, J. C., & Andrade, P. (2021). Target-specific effects of deep brain stimulation for Tourette syndrome: a systematic review and meta-analysis. *Frontiers in Neurology*, *12*, 769275. Doi: 10.3389/fneur.2021.769275

Target-specific effects of Deep Brain Stimulation for Tourette syndrome: A systematic review and meta-analysis

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Abbreviated title: Review of DBS in Tourette Syndrome

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Author contributions: The study has been designed by LW, TS, VV-V, JB, and PA. The literature search was conducted and data have been extracted by LW and JK. Data have been analyzed and interpreted by LW, TS, JB, and PA. The manuscript has been drafted by LW. Figures have been created by LW and PH. All authors revised and edited the manuscript.

Acknowledgements: This study was supported by the German Research Foundation (SFB 1451, Project ID 431549029-C07) and the Marga und Walter Boll Stiftung (210-06-16).

Abstract

Background: Extended research has pointed to the efficacy of deep brain stimulation (DBS) in treatment of patients with treatment-refractory Tourette syndrome (TS). The four most commonly used DBS targets for TS include the centromedian nucleus–nucleus ventrooralis internus (CM-Voi) and the centromedian nucleus–parafascicular (CM-Pf) complexes of the thalamus, and the posteroventrolateral (pvIGPi) and the anteromedial portion of the globus pallidus internus (amGPi). Differences and commonalities between those targets need to be compared systematically.

Objective: Therefore, we evaluated whether DBS is effective in reducing TS symptoms and target-specific differences.

Methods: A PubMed literature search was conducted according to the PRISMA guidelines. Eligible literature was used to conduct a systematic review and meta-analysis.

Results: In total, 65 studies with 376 patients were included. Overall, Yale Global Tic Severity Scale (YGTSS) scores were reduced by more than 50 in 69% of the patients. DBS also resulted in significant reductions of secondary outcome measures, including the total YGTSS, modified Rush Video-Based Tic Rating Scale (mRVRS), Yale-Brown Obsessive Compulsive Scale (YBOCS), and Becks Depression Inventory (BDI). All targets resulted in significant reductions of YGTSS scores and, with the exception of the CM-Pf, also in reduced YBOCS scores. Interestingly, DBS of pallidal targets showed increased YGTSS and YBOCS reductions compared to thalamic targets. Also, the meta-analysis including six randomized controlled and double-blinded trials demonstrated clinical efficacy of DBS for TS, that remained significant for GPi but not thalamic stimulation in two separate meta-analyses.

Conclusion: We conclude that DBS is a clinically effective treatment option for patients with treatment-refractory TS, with all targets showing comparable improvement rates. Future research might focus on personalized and symptom-specific target selection.

Keywords: Tourette syndrome, tic disorders, deep brain stimulation, DBS, neuromodulation, systematic review, meta-analysis

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics. Tics have an onset in childhood and reach their peak between 10 and 12 years of age (1). A majority of patients experience reduced symptoms by late adolescence or early adulthood. Nevertheless, around 20% of patients continue to experience persistent, distressing, and even painful tics throughout adulthood (2). Tics can have a great influence on the patient's overall health and well-being, as they may disrupt daily functioning and adversely affect the quality of life (3, 4). The pathophysiology of TS is related to disturbances of a complex neural network with dysregulations of the cortico-basal ganglia-thalamo-cortical (CBGTC) circuits being of predominant importance (5-9). The sensorimotor circuit, but also the limbic and associative circuits are implicated in the heterogenous pathophysiology of TS (5, 10-12). Therefore, TS is in many cases accompanied by comorbidities such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or depression (13, 14). Importantly, comorbid disorders are associated with increased social problems and reduced quality of life (15). Conventional treatment approaches for TS include pharmacological and behavioral therapy that are beneficial for a majority of patients (16-19). Nonetheless, some patients do not respond to these treatments and remain severely affected. An alternative and safe treatment option for those treatment-refractory patients constitutes deep brain stimulation (DBS) (20).

In 1999, DBS for TS was introduced by Vandewalle et al. (21). The original target chosen by this group was the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus complex (CM-Spv-Voi), informed by the experiences of Hassler and Dieckmann (22) with stereotactic thalamic lesions in this region. Thereafter, different targets have been selected based on the involvement of the CBGTC-circuits in TS pathophysiology. The most commonly used targets for TS include different thalamic nuclei and the globus pallidus internus (GPi). Within the thalamus, the centromedian nucleus–nucleus ventrooralis internus (CM-Voi) and the centromedian nucleus–parafascicular (CM-Pf) complexes have been used most frequently. This was motivated by their diverse connections to subcortical and cortical regions, including motor, associative and limbic areas (23-25). The GPi consists of an anteromedial part (amGPi), which is densely connected with associative and limbic networks, and a posteroventrolateral part (pvlGPi), which mainly projects to sensorimotor areas (26, 27). Based on this differentiation, it can be assumed that the pvlGPi may be particularly effective in reducing tic symptoms, while the amGPi might be especially effective for the treatment of comorbid OCD symptoms (28-32). The selection of an ideal target for TS treatment is still a

matter of debate and differences regarding clinical relevance remain unclear (33-38). Beyond that, target selection is complicated by the fact that the mechanism of action of DBS is still not fully understood, although, there is a growing consensus among researchers that DBS may exert its therapeutic effects by modulating the activity of widespread networks (20, 39-41). To date, the target choice is often a matter of preference of the centers, based on their surgical experience (42). On the contrary, some researchers have emphasized the idea that target selection should ideally be based on the individual characteristics of each patient. Hence, the patient's individual symptomatology and possible comorbid disorders should be taken into account in order to decide on the most appropriate target (34, 43).

Our objective was to examine the clinical effects of DBS for TS treatment with a systematic review and meta-analyses. First, we aimed to evaluate whether DBS is capable of reducing TS symptoms in the long-term. Our second goal was to evaluate whether the most commonly used targets, namely the CM-Voi, CM-Pf, the amGPi, and the pvlGPi, lead to different clinical outcomes regarding tic reduction and comorbid OCD symptoms.

Methods

Systematic Literature Search

A systematic literature search was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (44). A search of the electronic database of PubMed was performed to identify the existing literature investigating the effects of DBS in TS patients. The search terms included "Tourette syndrome OR Gilles de la Tourette syndrome OR Tourette´s disorder OR Tic disorder" AND "Deep Brain Stimulation OR DBS". Literature search was narrowed to all available articles published from January 1st 1999 to July 8th 2021. Additionally, two recently published meta-analyses of Baldermann et al. (36) and Xu et al. (38) were screened for additional research articles. In order to be included, studies were required to meet the following conditions: [1] case report, case series, clinical trial, or randomized controlled study of DBS for patients diagnosed with TS or a tic disorder; [2] original, published and peer-reviewed; [3] written in English. Studies were excluded if [1] clinical data of the patients could not be identified, [2] the clinical outcome was not assessed by the Yale Global Tic Severity Scale (YGTSS), or [3] patients had already been described in other articles. Titles and abstracts in each study from the search results were independently screened for eligibility by two researchers (LW and JK).

Data Extraction

The full text of the screened articles was further checked for eligibility and compliance with selection criteria by two researchers (LW and JK). If necessary, exclusion of duplicates was ensured by screening the patient demographics in the studies. Then, the following data were extracted from all studies included in the quantitative synthesis: first author name and publication year, number of participants, sex, age at surgery, DBS targets, follow-up (FU) range, pre- and post-surgery scores of the global YGTSS, total YGTSS, modified Rush Video-Based Tic Rating Scale (mRVRS), Yale-Brown Obsessive Compulsive Scale (YBOCS), and Becks Depression Inventory (BDI). When possible, individual patient data was gathered from the constituent studies. If two targets were evaluated in one patient, an additional case was added.

Study Quality Assessment

The quality of each study was assessed using the classifications scheme developed by French and Gronseth (45). This scheme includes 4 levels of evidence, with level 1 representing high-quality studies with low risk of bias and level 4 representing studies with a very high risk of bias. Additionally, the quality of randomized trials was assessed using the Cochrane risk of bias tool for randomized controlled trials (46). Two researchers independently evaluated the risk of bias of each study (LW and JK).

Statistical Analysis

The global YGTSS score (tic severity + impairment; range: 0-100, highest score representing worst clinical condition) served as primary outcome measure. Secondary tic-related outcome measures included the YGTSS total tic score (tic severity; range: 0-50), as well as the mRVRS. Additional secondary outcome measures included YBOCS and BDI assessments. Cases were weighted by the number of participants included in each individual study. Pre- and post-surgery primary outcome scores were compared using Wilcoxon signed-rank tests. Global YGTSS scores for maximum follow-up as well as for different postoperative time points (T1: $\leq$ 6 months; T2: $\leq$ 12 months; T3: >12 months) were compared with baseline scores (T0) across the whole sample. To examine whether YGTSS scores differed for the various postoperative time points Friedman's test was applied. In case of a significant result, post-hoc Dunn tests were conducted and Bonferroni-corrected for multiple comparisons. Regarding the secondary outcome measures, last reported YGTSS total tic, mRVRS, YBOCS and BDI scores were compared with preoperative baseline scores using Wilcoxon signed-rank tests. Subgroup

analyses of YGTSS percentage change scores at T2 (6 - 12 months) were performed using Kruskal-Wallis tests in order to compare the four targets (CM-Pf, CM-Voi, amGPi, and pvlGPi). T2 was chosen as time point for the subgroup analysis because of its clinical relevance and temporal precision compared to T3 and maximum follow-up. Post-hoc pairwise comparisons using the Dunn-Bonferroni approach were performed in the case of significant results. Furthermore, absolute change scores of the YBOCS at maximum follow-up were compared between the four targets using Kruskal-Wallis tests. For the YBOCS scores, maximum follow-up was chosen as time point for the subgroup analysis, because a temporal categorization was not possible due to insufficient data. Again, post-hoc Dunn tests were performed in case of significant results and Bonferroni-corrected for multiple comparisons. Of note, articles were excluded from subgroup analyses if the target was not appropriately specified, or multiple targets were used and outcomes combined. Beyond that, three separate meta-analyses of randomized controlled and double-blinded trials (RCTs) were conducted with the YGTSS total tic score as primary outcome measure. A first meta-analysis was performed to examine the general effect of DBS across all targets. In addition, two separate meta-analyses were conducted including RCTs targeting the thalamus and GPi, respectively. Standardized means of the YGTSS total tic score were compared between the experimental condition (DBS ON) versus control condition (DBS OFF). A random-effect model was used to account for heterogeneity among studies. Analyses were performed with SPSS 27 and the Review Manager 5.4.1. (47, 48). Significance levels were set at $p < 0.05$.

Results

Study Selection

The PubMed search of the existing literature on the clinical outcome of DBS in TS patients identified 479 articles. In addition, the meta-analyses by Baldermann et al. (36) and Xu et al. (38) yielded 57 and 29 studies, respectively. After removing duplicates ($n = 75$), abstracts were screened for the above mentioned selection inclusion criteria, which resulted in the exclusion of 397 records. Full texts of the remaining 93 articles were subsequently checked for eligibility. Among these, 18 articles were excluded because the clinical outcome was not assessed using the YGTSS or YGTSS change was not sufficiently reported (e.g., only improvement rates without baseline values). Thereafter, additional 10 studies were excluded after a thorough analysis, because the study participants had already been reported in other articles. In total, 65 studies were included, of which 58 studies were case reports or case series with an evidence

level of four (45). Seven reports were randomized, double-blinded controlled trials, with an evidence level of three. The majority of RCTs had an overall low risk of bias, except for two RCTs, which had some concerns (see details in **Supplemental Figure 1**). One RCT needed to be excluded because YGTSS scores were only reported for the stimulation ON setting, but not for the stimulation OFF setting. Another RCT was already excluded during the full text screening, because only percentage changes were reported without raw baseline and follow-up scores. An adapted PRISMA flow diagram is displayed in **Figure 1**.

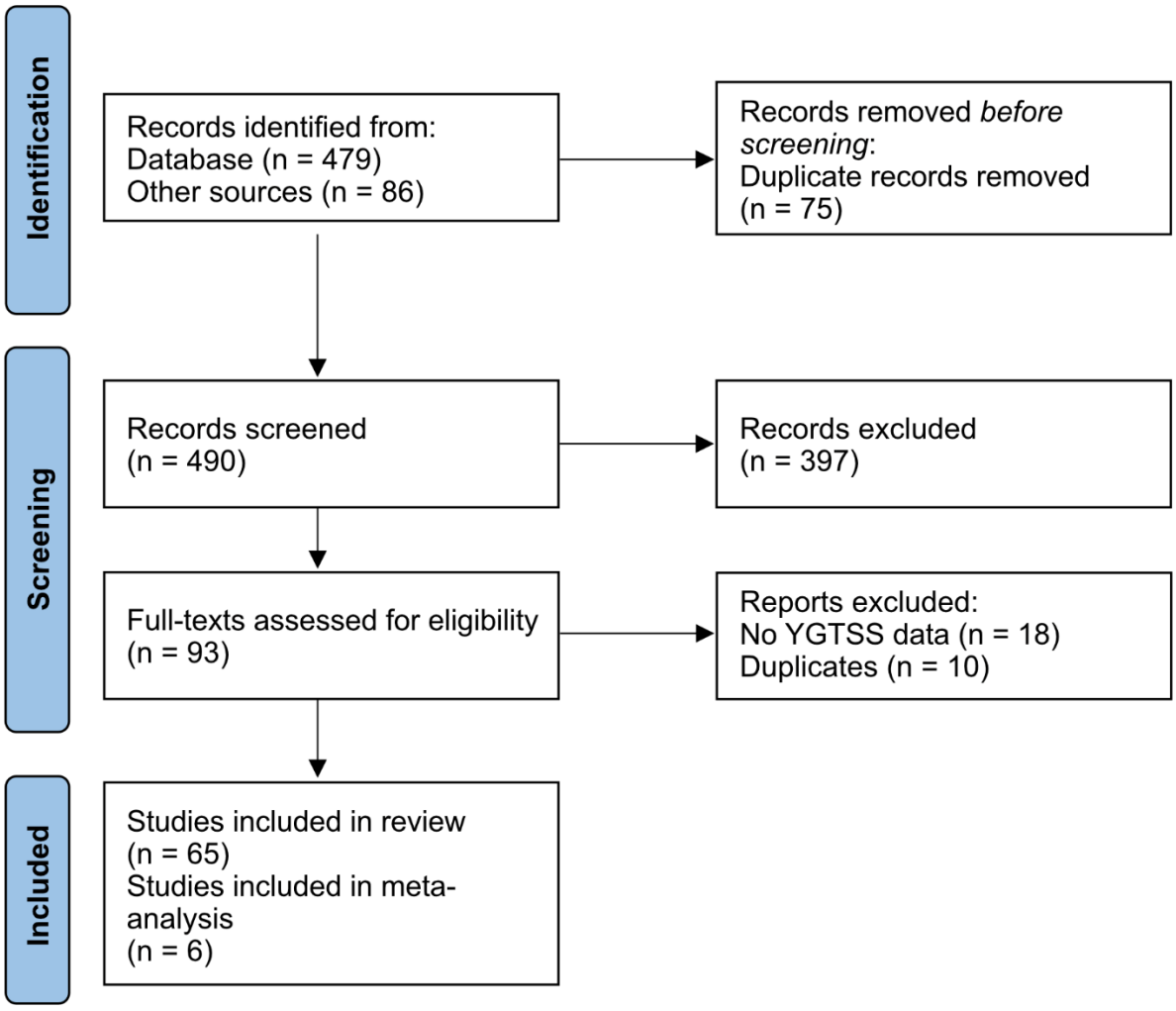

Figure 1: Adapted PRISMA 2020 Flow Diagram (44).

Individual Participant Data

In total, 65 studies with 376 patients were included in the final analysis (see **Table 1** for a detailed overview of the included studies). Most of the included patients were male (75.63%) and the median age was 30.5 years (range: 15-50 years). Of those 376 patients, 96 (25.53%) were stimulated in the CM-Voi, 59 (15.69%) in the CM-Pf, 100 (26.6%) in the amGPi, and 81 (21.54%) in the pvlGPi. The four targets are visualized in **Figure 2**.

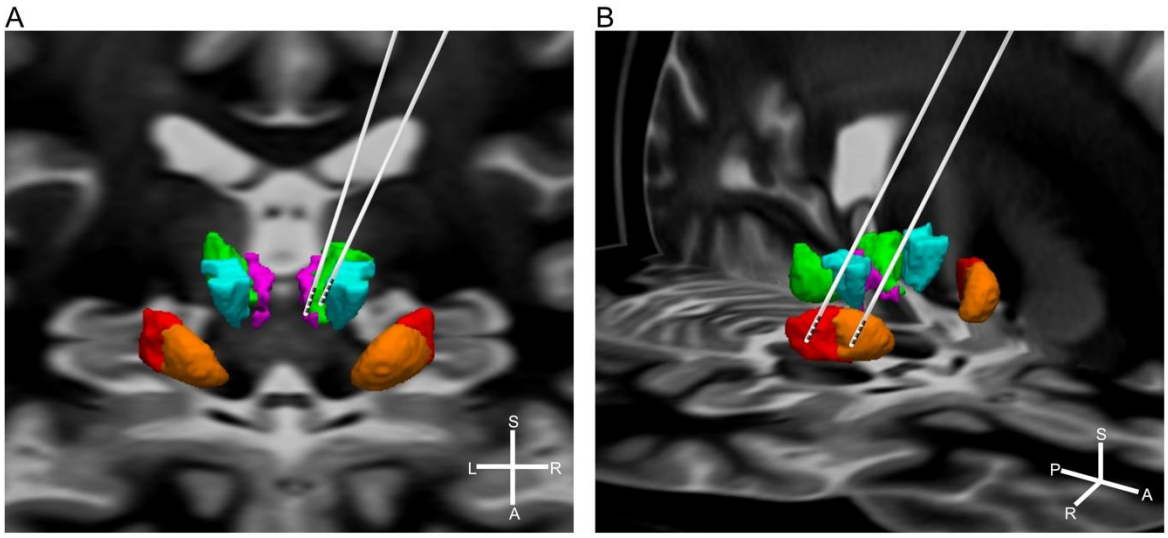

Figure 2: Simplified visualization of DBS electrodes of the different targets. Shown are the target regions: green = CM; purple = Pf; turquoise = Voi; red = pvlGPi; orange = amGPi. For illustration purposes targets are displayed unilateral only. **(A)** Thalamic targets: left electrode = CM-Pf; right electrode = CM-Voi. Background shows the coronal section of a brain MRI. **(B)** Pallidal targets: left electrode = pvlGPi; right electrode = amGPi. Background shows the horizontal section of a brain MRI. Graphics were generated using the DISTAL atlas (120) and MNI PD25 atlas (121). Abbreviations: S = superior, A = anterior, L = left, R = right.

The ventral anterior/ventrolateral thalamus (VA/VL) was targeted in 11 patients (2.93%). In four patients, the thalamus was indicated as target, but not further specified. Similarly, in one case, the GPi without further specification was reported as the target. In two cases, both amGPi and pvlGPi were stimulated. The anterior limb of internal capsule/nucleus accumbens (ALIC/NAc) was targeted in eight patients (2.13%). In two other cases electrodes were implanted in the globus pallidus externus (GPe). A total of 12 patients received electrodes in two target areas. In two patients the thalamus and pvlGPi were targeted; however, the thalamus was not further specified. The CM-Voi and ALIC/NAc were targeted in three patients, while the CM and ALIC/NAc were targeted in one patient. Electrodes in both the amGPi and ALIC/NAc were implanted in two patients and three patients received electrodes in both the

pvlGPi and the subthalamic nucleus (STN). In one patient, electrodes were implanted in the region of the ALIC and the bed of the nucleus of stria terminalis. In another two patients the fields of forel (subthalamus) were targeted. Although most patients received bilateral DBS, six patients underwent unilateral DBS in the pvlGPi and one patient in the amGPi.

Table 1: Overview of included studies (n = 65).

References	Level of evidence	N	Target(s)	Follow-up	Primary outcome measure	Mean improvement %
Diedrich et al. (49)	4	1	pvlGPi	14 mo	YGTSS100	46.99
Bajwa et al. (50)	4	1	CM-Spv-Voi	24 mo	YGTSS50	63.64
Kuhn et al. (51)	4	1	ALIC/NAc	30 mo	YGTSS100	41.11
Maciunas et al. (52)	3	5	CM-Pf	3 mo	YGTSS100	43.60
Shahed et al. (53)	4	1	pvlGPi	12 mo	YGTSS100	73.33
Shields et al. (54)	4	1	CM	3 mo	YGTSS100	45.57
Dehning et al. (55)	4	4	pvlGPi	5-12 mo	YGTSS100	41.32
Kuhn et al. (56)	4	1	ALIC/NAc	10 mo	YGTSS100	51.85
Neuner et al. (57)	4	1	ALIC/NAc	36 mo	YGTSS100	44.00
Servello et al. (58), Servello et al. (59) *	4	6	Voi/CM-Pf (2), ALIC/NAc (1), Voi/CM-Pf + ALIC/NAc (3)	10-34 mo	YGTSS100	49.12
Burdick et al. (60)	4	1	ALIC/NAc	30 mo	YGTSS50	-14.81
Marceglia et al. (61)	4	7	Voi/CM-Pf	6-48 mo	YGTSS100	33.01
Ackermans et al. (62)	3	6	CM-Spv-Voi	12 mo	YGTSS50	47.62
Pullen et al. (63)	4	1	CM-Pf	18 mo	YGTSS100	94.81
Kaido et al. (64)	4	3	CM-Pf-Voi	12 mo	YGTSS100	36.14
Kuhn et al. (65)	4	2	VA/VL	12 mo	YGTSS100	85.98
Lee et al. (66)	4	1	CM-Pf	18 mo	YGTSS100	58.43
Martinez-Fernandez et al. (67) *	4	6	amGPi (3), pvlGPi (3)	3-24 mo	YGTSS100	24.92
Rzesnitzek et al. (68)	4	1	CM-Pf	13 mo	YGTSS100	83.12
Savica et al. (69)	4	3	CM-Pf	12 mo	YGTSS100	69.73

Table 1: Continued

References	Level of evidence	N	Target(s)	Follow-up	Primary outcome measure	Mean improvement %
Dong et al. (70)	4	2	pvlGPi (unilateral)	12 mo	YGTSS100	55.88
Duits et al. (71)	4	1	CM-Spv-Voi	23 mo	YGTSS50	7.14
Sachdev et al. (72)	4	1	ALIC/NAc	7 mo	YGTSS100	79.37
Massano et al. (73)	4	1	amGPi	24 mo	YGTSS100	60.49
Motlagh et al. (74)	4	8	Tha (4), pvlGPi (2), Tha + pvlGPi (2)	6 -107 mo	YGTSS50	39.80
Okun et al. (75)	3	5	CM	6 mo	YGTSS100	19.43
Piedimonte et al. (76)	4	1	GPe	6 mo	YGTSS100	70.51
Dehning et al. (77)	4	6	pvlGPi	12-60 mo	YGTSS100	68.06
Dong et al. (78)	4	1	pvlGPi	39 mo	YGTSS100	92.86
Huasen et al. (79)	4	1	amGPi	12 mo	YGTSS100	55.42
Nair et al. (29)	4	4	amGPi	3-26 mo	YGTSS100	90.96
Patel & Jimenez-Shahed (80)	4	1	GPi	6 mo	YGTSS100	52.81
Pourfar et al. (81)	4	1	CM-Spv-Voi	14 mo	YGTSS100	48.86
Sachdev et al. (82), Cannon et al. (83)	4	17	amGPi (15), amGPi + ALIC/NAc (2)	4-46 mo	YGTSS100	54.21
Zhang et al. (84)	4	12	pvlGPi	13-80 mo	YGTSS100	52.13
Kefalopoulou et al. (85), Morreale et al. (86)	4	15	amGPi (12), pvlGPi (2)	6 mo	YGTSS100	50.54
Wardell et al. (87)	4	4	amGPi	14-48 mo	YGTSS100	38.66
Cury et al. (88)	4	1	CM-Pf	18 mo	YGTSS100	70.53
Huys et al. (89)	4	8	VA/VL	12 mo	YGTSS100	55.75
Smeets et al. (90)	4	5	amGPi (4), GPe (1)	12-38 mo	YGTSS50	74.23
Testini et al. (91)	4	11	CM-Pf	2-91 mo	YGTSS100	51.97
Zhang et al. (92)	4	24	pvlGPi (4 unilateral)	12 mo	YGTSS100	57.84
Akbarian-Tefaghi et al. (93)	4	15	amGPi	17-82 mo	YGTSS100	45.45
Dwarakanath et al. (94)	4	1	amGPi	9 mo	YGTSS100	72.45
Neudorfer et al. (95)	4	2	FF H1	12-18 mo	YGTSS100	76.54

Table 1: Continued

References	Level of evidence	N	Target(s)	Follow-up	Primary outcome measure	Mean improvement %
Picillo et al. (96)	4	1	CM-Pf	12 mo	YGTSS100	7.69
Welter et al. (97)	3	16	amGPi	6-12 mo	YGTSS100	40.24
Azimi et al. (98)	4	6	amGPi	12 mo	YGTSS100	62.56
Doshi et al. (99)	4	2	amGPi	18 mo	YGTSS100	64.56
Dowd et al. (100)	4	12	CM-Pf-Voi	6-58 mo	YGTSS100	50.59
Kano et al. (101)	4	2	CM-Pf-Voi	29-35 mo	YGTSS100	34.13
Richieri et al. (102)	4	1	VA/VL	48 mo	YGTSS50	74.36
Brito et al. (103)	4	5	CM-Pf	12 mo	YGTSS100	30.00
Kakusa et al. (104)	4	1	CM + ALIC/NAc	12 mo	YGTSS100	84.29
Rossi et al. (105)	4	1	amGPi (unilateral)	26 mo	YGTSS100	87.10
Zhang et al. (106)	4	1	pvlGPi	3 mo	YGTSS100	53.19
Zhang et al. (107)	4	10	pvlGPi	24-96 mo	YGTSS100	81.43
Zhu et al. (108)	4	3	pvlGPi + STN	6 mo	YGTSS100	36.60
Duarte Batista et al. (109)	4	1	ALIC/BST	12 mo	YGTSS100	81.00
Servello et al. (30, 58, 110, 111), Porta et al. (112,113), Marceglia et al. (114)	4	57	Voi-CM-Pf (41), amGPi (14), ALIC/NAc (2)	24-48 mo	YGTSS100	38.94
Andrade et al. (115), Heiden et al. (32)	4	7	CM-Voi	6 mo	YGTSS100	42.22
Kimura et al. (116)	4	25	CM-Pf	36 mo	YGTSS100	56.59
Müller-Vahl et al. (117)	3	10	CM-Voi (4), pvlGPi (6)	8-108 mo	YGTSS50	26.96
Sun et al. (118)	4	6	pvlGPi	26-48 mo	YGTSS100	59.62
Baldermann et al. (119)	4	8	CM-Voi	12 mo	YGTSS100	47.73

Duplicate studies are mentioned. An additional case was added when two targets were evaluated in one patient (*). Abbreviations: N = Number of participants; mo = months; YGTSS100 = global YGTSS score; YGTSS50 = YGTSS total tic score; ALIC/NAc = Anterior limb of internal capsule/nucleus accumbens; GPe = Globus pallidus externus; STN = Subthalamic nucleus; FF H1 = H1 Field of Forel; Tha = Thalamus.

Clinical Outcomes Analysis

Global YGTSS scores for all targets combined were significantly reduced at maximum follow-up (n = 343, Z = -15.97, p < 0.001). The follow-up period ranged from 3 to 91 months (*Mdn* = 25 months). The median YGTSS score decreased from 79.92 points (*IQR* = 13.25) to a post-surgery median of 34.69 points (*IQR* = 20.93), which represents a median reduction rate of 56.59%. Also, 69.4% (n = 238) of the patients experienced a symptom reduction of more than 50% at maximum follow-up. Moreover, global YGTSS scores at different postoperative time points (T1: ≤ 6 months; T2: ≤ 12 months; T3: >12 months) differed significantly from postoperative baseline scores (T0). DBS resulted in a YGTSS median reduction of 34 points at T1 (n = 201, Z = -12.27, p < 0.001). At T2, global YGTSS scores were reduced by a median of 37 (n = 190, Z = -11.87, p < 0.001), whereas median scores decreased by 53.93 at T3 (n = 123, Z = -9.65, p < 0.001). Interestingly, clinical efficacy increased significantly over time after surgery. A Friedman's test showed a significant difference between global YGTSS scores at T0, T1, T2, and T3 (n = 73, $\chi^2(3) = 207.14$, p < 0.001). Dunn's post-hoc tests revealed that median YGTSS scores decreased from T0 to T1, from T1 to T2, and from T2 to T3 (T0: *Mdn* = 67.56, *IQR* = 10.44; T1: *Mdn* = 39.12, *IQR* = 6.18; T2: *Mdn* = 37.00, *IQR* = 2.25; T3: *Mdn* = 24.07, *IQR* = 0), which was statistically significant in all cases after Bonferroni adjustments (p < 0.001). YGTSS outcomes for the different time points are depicted in **Figure 3**.

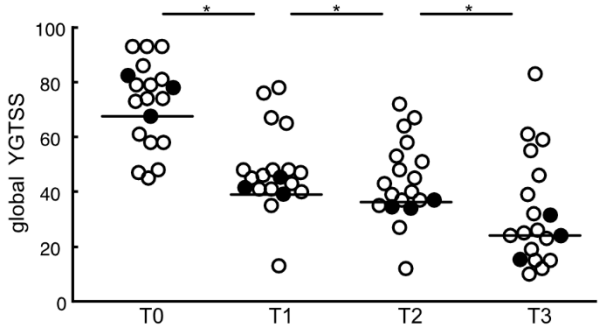

Figure 3: Scatterplots of global YGTSS scores for all targets combined at different postoperative time points (T0: baseline; T1: ≤ 6 months; T2: ≤ 12 months; T3: >12 months). Circles represent individual studies; color-filled circles represent more heavily weighted studies (more participants). Horizontal bars show the median values for each target. Significant differences between time points are indicated with asterisks (p < 0.05).

Analysis of secondary tic-related outcome measures revealed that the median of YGTSS total tic scores decreased from 39.12 points (*IQR* = 10) to 19.0 points (*IQR* = 13) at maximum follow-up (range: 3 to 107 months, *Mdn* = 12 months), which equals a median symptom reduction rate of 50.43% (n = 159, Z = -10.90, p < 0.001). Results for the MRVRS showed a

median reduction of 35.54% at maximum follow-up (Pre: *Mdn* = 14.00, *IQR* = 4.06; Post: *Mdn* = 9.00, *IQR* = 7.70, *n* = 64, *Z* = -6.57, *p* < 0.001). The follow-up period for the MRVRS ranged from 3 to 84 months (*Mdn* = 12 months). Regarding comorbid symptoms, the median of YBOCS scores decreased from 20 points (*IQR* = 10.82) to 11.45 points (*IQR* = 7.51) at maximum follow-up (range: 3–107 months, *Mdn* = 34 months), representing a median reduction rate of 43.23% (*n* = 206, *Z* = -11.84, *p* < 0.001). Of these patients, 68.4% (*n* = 141) experienced at least a 35% reduction of OCD, which is the criterion to be considered a responder (49). Finally, the BDI median score declined by a reduction of 50% from 25.70 points (*IQR* = 13.40) to 13.85 points (*IQR* = 11.30) at maximum follow-up, which ranged from 3 to 49.5 months (*Mdn* = 23.5 months). This reduction was also statistically significant (*n* = 110, *Z* = -7.71, *p* < 0.001).

Subgroup Analysis

Wilcoxon signed-rank tests revealed that stimulation of all targets resulted in a significant global YGTSS reduction after up to 12 months (see **Table 2**). Importantly, these target-specific YGTSS percentage changes differed significantly (*n* = 172, $\chi^2(3) = 21.41$, *p* < 0.001). Dunn's pairwise tests showed that the median YGTSS percentage change was significantly larger for pvlGPi compared to CM-Pf (*p* < 0.001) and CM-Voi (*p* = 0.006). Additionally, the median percentage change was significantly larger after amGPi compared to CM-Pf (*p* = 0.017). Other pairwise comparisons were not statistically significant. YGTSS outcomes for the different targets are depicted in **Figure 4**.

Table 2: Overview of global YGTSS outcomes for the different targets at T2 (6-12 months postoperatively).

Target	N	Pre-DBS Median	Post-DBS Median	Median Reduction	Median % Change	*p*-value
CM-Pf	36	79.92 (0.00)	43.80 (0.00)	36.12 (0.00)	45.20 (0.00)	< 0.001
CM-Voi	55	67.56 (0.00)	37.00 (0.00)	30.56 (0.00)	45.23 (0.00)	< 0.001
amGPI	20	76.33 (8.09)	28.67 (22.67)	47.33 (23.83)	62.45 (29.36)	< 0.001
pvlGPi	61	74.00 (8.40)	34.00 (3.55)	42.80 (15.50)	57.84 (13.40)	< 0.001

Measures of dispersion in brackets are interquartile ranges. P-values represents the results of Wilcoxon signed-rank tests comparing pre- and post-surgery global YGTSS scores at T2 for each target.

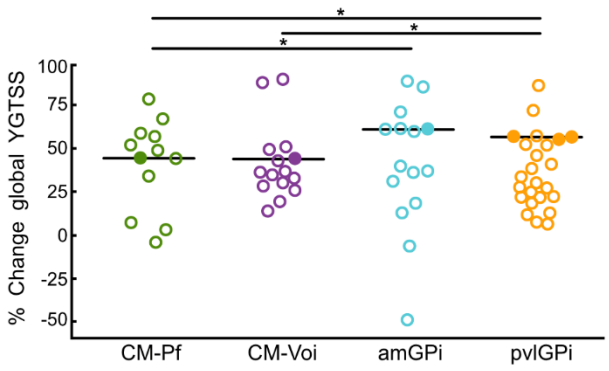

Figure 4: Scatterplots of global YGTSS percentage change scores for the different targets at T2 (6-12 months after DBS surgery). Circles represent individual studies; color-filled circles represent more heavily weighted studies (more participants). Horizontal bars show the median values for each target. Significant differences between targets are indicated with asterisks ($p < 0.05$).

Furthermore, Wilcoxon signed-rank tests showed that stimulation of the CM-Voi, amGPi, pvlGPi, but not the CM-Pf resulted in a significant reduction of YBOCS scores at maximum follow-up (range: 3–84 months, *Mdn* = 48 months) (see **Table 3**). Importantly, only 3 studies were included in the CM-Pf target group (n = 11) with a maximum follow-up period of 6 months. Subgroup analysis of the YBOCS absolute change scores showed significant differences across targets, as determined by a Kruskal-Wallis test ($n = 143$, $\chi^2(3) = 26.58$, $p < 0.001$). Bonferroni corrected post-hoc analysis indicated that the median YBOCS absolute change after pvlGPi stimulation was significantly higher than after CM-Voi DBS ($p = 0.004$) and CM-Pf DBS ($p < 0.001$). Additionally, the median absolute change was significantly greater for amGPi DBS compared to CM-Pf DBS ($p = 0.011$). Other pairwise comparisons were not statistically significant. YBOCS outcomes for the different targets are depicted in **Figure 5**.

Table 3: Overview of YBOCS outcomes for the different targets after DBS surgery at maximum follow-up.

Target	N	Pre-DBS Median	Post-DBS Median	Median Reduction	Median % Change	*p*-value
CM-Pf	11	17.60 (5.00)	7.00 (11.60)	5.60 (6.60)	44.44 (50.13)	0.102
CM-Voi	73	20.17 (3.17)	11.45 (0.45)	8.72 (2.92)	43.23 (0.00)	< 0.001
amGPI	36	19.50 (11.43)	10.69 (4.12)	11.50 (15.55)	55.17 (46.42)	< 0.001
pvlGPi	23	24.70 (7.00)	3.20 (9.30)	16.50 (10.50)	87.04 (30.15)	< 0.001

Measures of dispersion in brackets are interquartile ranges. P-values represents the results of Wilcoxon signed-rank tests comparing pre- and post-surgery YBOCS scores at maximum follow-up for each target.

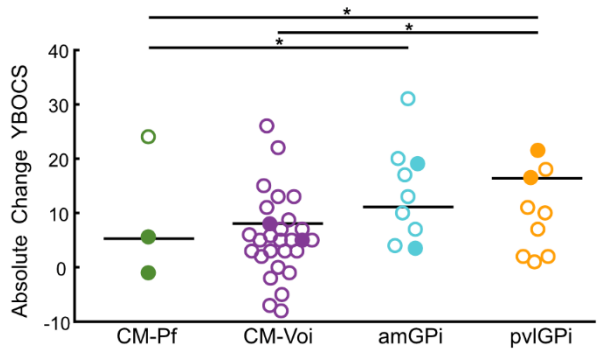

Figure 5: Scatterplots of YBOCS absolute change scores for the different targets at maximum follow-up. Circles represent individual studies; color-filled circles represent more heavily weighted studies (more participants). Horizontal bars show the median values for each target. Significant differences between targets are indicated with asterisks ($p < 0.05$).

Meta-Analyses

Three separate meta-analyses of randomized controlled and double-blinded trials were conducted with the YGTSS total tic score as primary outcome measure (see **Figure 6**). The first meta-analysis, which included six studies (FU range = 0,23–6 months, *Mdn* = 3 months), showed a significant overall effect of the experimental condition (DBS ON) over the control condition (DBS OFF) for thalamus and GPi targets combined. The test of heterogeneity was not significant, and the overall effect size was -0.66 (CI: -1.10, -0.22). The second meta-analysis for thalamic DBS included four studies with a total of 27 patients in the experimental group and 25 patients in the control group (FU range = 0,23–6 months, *Mdn* = 3 months). The test for the overall effect was not significant at 0.05 level ($p = 0.07$), indicating that YGTSS tic scores did not significantly differ between the experimental and control condition. The overall effect size was -0.72 (CI: -1.50, 0.06). In the contrary, results of the third meta-analysis for pallidal DBS (FU = 3 months) showed a significant overall effect of GPi DBS ($p = 0.02$), favoring stimulation ON over stimulation OFF. A non-significant heterogeneity and overall effect size of -0.66 (CI: -1.20, -0.12) were observed.

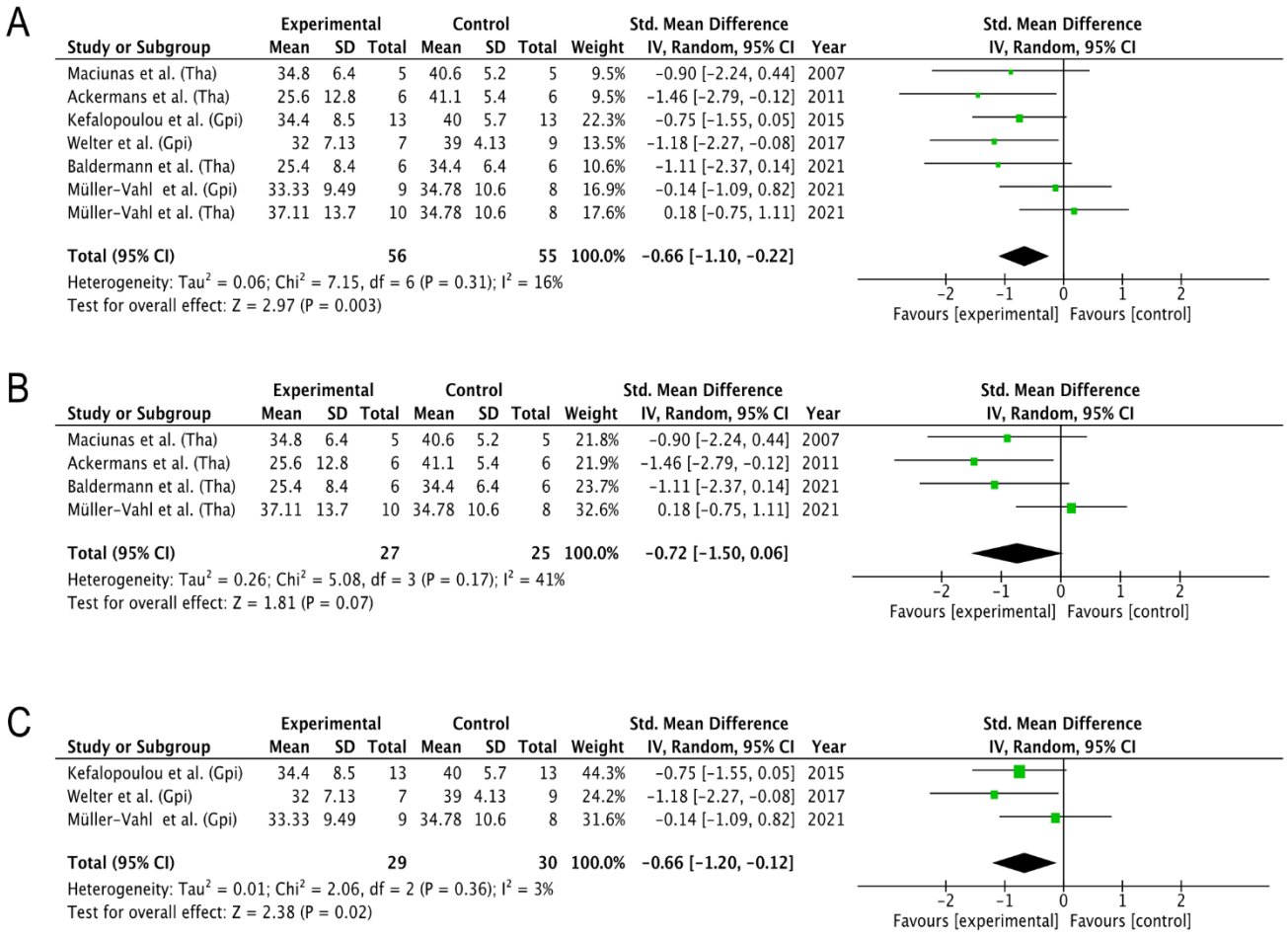

Figure 6: Forest plots of RCTs. Mean YGTSS total tic scores were compared between experimental conditions (DBS ON) versus control conditions (DBS OFF). **(A)** General effect of DBS for both thalamic and pallidal targets. **(B)** Effect of DBS for thalamic targets. **(C)** Effect of DBS for pallidal targets. Targets were not further specified. Graphics were created with the Review Manager 5.4.1. (48). Abbreviations: GPi = globus pallidus internus, Tha = thalamus, CI = confidence interval.

Discussion

Summary of Main Findings

Here, we provide an up-to-date overview of the existing literature to examine the clinical efficacy of DBS in patients with TS. Analysis of global YGTSS scores of 343 individual patients revealed that DBS of all targets combined is capable of reducing TS symptomatology. At maximum follow-up, two-thirds of patients experienced a symptom reduction of more than 50%. Considering the time course of symptom improvement after DBS-surgery, our results show that global YGTSS scores were already reduced after six months. Importantly, thereafter the clinical benefits of DBS increased even further. Moreover, the present results revealed that DBS resulted in significant reductions of other tic-related outcome measures (MRVRS, YGTSS total tic score) as well as comorbidities (YBOCS, BDI). The meta-analysis of six RCTs including thalamic and pallidal targets further confirmed the clinical efficacy of DBS.

Additionally, we compared the clinical outcomes of the most commonly used DBS targets, namely CM-Pf, CM-Voi, amGPi, and pvlGPi. Stimulation of all targets resulted in a significant reduction of global YGTSS scores between 6 and 12 months. However, stimulation of the GPi led to an even larger reduction rate of tic symptoms compared to thalamic stimulation. Specifically, pvlGPi DBS showed higher reduction rates of global YGTSS scores compared to CM-Pf and CM-Voi DBS. Reduction rates were also greater for amGPi DBS compared to CM-Pf DBS. Results of the two separate meta-analyses revealed a significant effect for GPi stimulation, but not for thalamic stimulation. Moreover, stimulation of all targets except for the CM-Pf resulted in a significant reduction of YBOCS scores at maximum follow-up. Also, pvlGPi DBS led to increased OCD symptom reduction compared to CM-Pf and CM-Voi DBS at maximum follow-up. Similarly, stimulation of amGPi led to increased OCD symptom reduction compared to CM-Pf stimulation.

Interpretation of Main Findings

Based on the present results, we suggest that DBS is capable of reducing TS symptomatology in patients with treatment-refractory TS, which is in line with previous research (36, 37, 123). DBS significantly reduces tic-related symptoms as well as comorbid OCD and affective symptoms in TS patients. The latter finding is of great importance, since it is common that patients with TS exhibit at least one comorbid disorder (3, 15, 124). Moreover, time appears to play an important role in DBS for TS, as the beneficial effects of DBS seem to increase up to more than one year after surgery. Recent evidence implicates that this is not the case with

conservative therapies, including pharmacological and behavioral therapy, which effects tend to decline over time (123). The individual optimization of stimulus parameters, especially during the first 6 months after surgery, likely contributes to this particular time course of DBS effects (74). Of note, our results are mainly based on the analysis of case reports or case series with an evidence level of four (45). The meta-analysis for all targets combined, which also pointed to the efficacy of DBS in TS, included only six RCTs with several limitations including a high heterogeneity in terms of time frame, procedure, outcome measures and target selection. In order to move away from the experimental use of DBS for TS patients, additional randomized controlled and double-blinded trials are needed. At the same time, RCTs with larger cohorts are almost impossible in TS because the number of candidates for DBS may not be sufficient. Nevertheless, future RCTs should strive to use consistent and comparable study designs.

Importantly, the present results demonstrate that stimulation of all targets lead to a significant tic reduction following DBS surgery. Similarly, stimulation of all targets except for the CM-Pf result in significant reductions of OCD symptoms. Results of the subgroup analyses also indicate that the clinical outcomes of DBS differ among the four targets. However, these results should be interpreted with great caution due to several reasons. On the one hand, we cannot rule out the possibility that the results of the subgroup analysis are influenced by our categorization of the individual targets. We have tried to categorize the targets as accurately as possible based on the description of the target locations in the original articles. However, especially in the two thalamic target groups, the individual targets within a categorization are likely to vary, because of the size as well as the complex nomenclature of the thalamus (125, 126). Also, even if authors specify the same surgical target, targets can still be slightly different. For example, personal correspondences showed that the CM-Voi target used by Servello et al. (127) is located 2mm further anterior to the CM-Voi target of Visser-Vandewalle et al. (21, 110). Additionally, the actual volume of tissue activated (VTA) is highly dependent on factors such as the exact electrode position, stimulation settings, and individual anatomy. Furthermore, it cannot be ruled out that the results are confounded by a systematic bias in patient selection. Because of the relatively small sample sizes in target groups, clinical outcomes may be influenced by the patient selection of a single center, as patient selection processes may differ from site to site. Certain selection criteria, such as age, tic severity and impairment were shown to significantly influence clinical outcomes after DBS (36). Regarding the post-surgery time periods included in our analyses, it should be kept in mind that tic reduction rates after 6 to 12 months were compared between targets; meaning that the present analysis of the YGTSS

showed differences between the targets up to one year after surgery. On the contrary, for the YBOCS, targets were compared at maximum follow-up, ranging from 3 to 84 months, which is a very broad time period. Similarly, studies included in the meta-analysis for thalamic DBS ranged from 7 days to 6 months, which is still a broad time period. Based on the present findings, one may argue that it is challenging to compare such temporally heterogeneous results.

Nonetheless, results of the subgroup analyses particularly emphasize the high capability of pallidal DBS to reduce tic symptoms up to one year following DBS surgery. In line with our findings, pvlGPi has proven to be an effective target for patients with other motor dysfunctions, such as Parkinson's disease and dystonia (33, 128-130). Therefore, the pvlGPi is also preferably chosen for DBS in TS patients with dystonic tics (67, 85). Given its anatomical connections to sensorimotor regions, the modulation of these fibers seems like a probable mechanism of action for pvlGPi DBS (28, 32). However, stimulation of projections from pvlGPi to sensorimotor networks was found to correlate negatively or not at all with tic improvement (31, 131). The amGPi was previously thought to be a particularly effective target for TS patients with comorbid OCD symptoms, but according to the present results, it may also play an equally important role in tic reduction (30). In line with this, registry data demonstrated that amGPi DBS resulted in the greatest tic improvement after one year compared to CM, pvlGPi and ALIC DBS; however, differences between targets were not significant (37). Concurrently, connectivity from the amGPi to limbic and associative networks positively correlated with tic improvement (31, 131). Interestingly, activation of the sensorimotor pallido-subthalamic pathway was more predictive of OCD symptom improvement compared to the associative pallido-subthalamic pathway (131). This agrees with our findings, which demonstrated the high capability of pvlGPi and amGPi DBS in reducing OCD symptoms. Surprisingly, the current findings partly differ from what we know from previous reports and are not entirely consistent with the functionally distinction of sensorimotor, associative, and limbic pathways. It should be noted that TS is no pure motor disorder (132). Heterogeneity and complexity of the disorder might partly explain the tic improvement following amGPi DBS and OCD symptom improvement after pvlGPi DBS (131, 133). Additionally, the different targets might improve TS symptomatology through different functional mechanisms, such as direct inhibition of tic execution or enhancement of the ability to suppress tics (134, 135). However, the exact causal relationships are not understood, and further research is needed to explain this inverse differentiation of the pallidal DBS targets.

Beyond that, the present results suggest that thalamic DBS yields lower tic reduction rates compared to pallidal DBS up to 12 months postoperatively. To our knowledge, no significant differences have to date been found between targets in terms of tic reduction rates (36-38, 136). Only a few studies compared the clinical effects of thalamic stimulation with those of pallidal stimulation, which indeed pointed to a superior effect of the latter, but only up to 3 months (117, 137, 138). However, as our findings show, it may take at least one year for the positive effects of DBS to fully develop. Accordingly, YGTSS reduction was shown to be greater at least one year after CM-Pf DBS compared to less than one year (91). Moreover, although the initial positive effects of GPi DBS have been shown to decrease several years after surgery, the beneficial effects from CM-Voi DBS were ongoing in a subset of patients (117, 139). Based on this, we cannot rule out differences in clinical time courses between targets, but long-term results are rare and further investigations are needed. Apart from that, results of our meta-analysis revealed a non-significant effect of DBS for thalamic targets. It should be noted that this finding was predominantly shaped by a single RCT favoring stimulation OFF over stimulation ON, which was weighted with 32,6% (for details see **Figure 6)**. According to the authors, results of this trials might be influenced by poor compliance, placebo effect, and high infection rate (117). Also, in three patients, electrode positions did not correspond to the planned target point and extended into subthalamic regions, which in turn may have compromised optimal stimulation settings, eventually resulting in under-stimulation (117). Furthermore, our results revealed that thalamic DBS targets are less capable of alleviating OCD symptoms than pallidal targets. In particular, CM-Pf DBS was found to have no effect at all. This result is rather surprising, because of the connections between the CM-Pf and limbic regions, especially the nucleus accumbens (23-25). However, it should be noted that only 3 studies were included in the CM-Pf target group (n = 11) with a maximum follow-up period of 6 months. As already discussed above, the results are also highly dependent on the patient selection and the type and severity of the OCD symptoms. Centers tend to target the amGPi or ALIC/NAc for patients with more severe OCD symptoms, while CM-Pf is preferably chosen for patients with predominant tic symptoms (140).

Finally, it needs to be mentioned that despite the effectiveness of the various DBS targets, other factors also play a role in the selection of targets. In the present review, no differences in side effects between the targets have been taken into account, because a quantitative evaluation of adverse events was not feasible due to lack of information. Ideally the safety of DBS should also be assessed in the same way. Side effects may vary across the four targets, which could influence the final decision on target selection for DBS of individual

patients. Some other technical details are also not considered, such as the substantial amount of total energy needed for GPi stimulation compared to thalamic stimulation, which may result in reduced battery life duration, leading to more frequent battery replacements in the case of non-rechargeable implanted pulse generators (141).

To sum up, it should be emphasized that the present results do not provide an answer to the question of which target is more clinically relevant for the treatment of TS. Rather, they highlight the importance of considering which target might be the best choice for the individual patients based on specific symptoms and individual characteristics. Future studies might focus on defining precise criteria and guidelines for the target selection for DBS in TS.

Future Directions for DBS Targeting in TS

Connectomic DBS represents a unique opportunity to guide target selection in psychiatric disorders that are heterogenous, such as Tourette Syndrome (39, 142, 143). The application of DTI tractography has the great potential to shift the focus away from identifying one appropriate target for TS and instead enable for personalized and symptom-specific targeting. Specifically, a connectomic approach may allow to display the fiber pathways associated with specific symptom improvement. Identification of such connectivity patterns could potentially lead to the optimization of targets or discovery of new targets. Several studies have investigated structural connectivity patterns in DBS for TS (31, 32, 103, 115, 131, 144). Importantly, studies showed that the VTA of the target alone did not predict the clinical efficacy of DBS for TS (103, 145). Instead, results of several studies indicated that the connectivity between the VTA and cortical regions was linked to the clinical outcome after DBS in TS patients (31, 32, 103, 145). However, the various targets used for DBS in TS show different connectivity profiles, and cortical networks linked to clinical improvement have been shown to differ across targets (31, 32). In particular, networks positively correlated with tic improvement included limbic and associative regions for the GPi, and sensorimotor as well as parietal-temporal-occipital regions for the thalamus. For both targets, connectivity to the cerebellum also correlated positively with tic improvement (31). This suggests that stimulation of the different targets does not result in the modulation of a single network. Rather, stimulation of the different targets might result in the modulation of distinct, maybe partly overlapping networks, which then lead to the improvement of specific symptoms via a certain functional mechanism. DBS should aim to target those symptom-specific networks, thereby allowing to treat the entire complex spectrum of TS symptoms. Further studies examining the clinical outcomes of DBS in TS with known targets using structural imaging techniques are needed to improve our understanding of

the underlying DBS mechanisms and to increase the efficacy of target selection. Particularly, there is a need for studies that identify fiber pathways associated with improvement of various TS symptoms, including simple tics, complex tics, the premonitory urge, comorbid symptoms, as well as tic suppression. In addition, the functional mechanisms by which modulation of the network ultimately improves tic symptoms (e.g., by directly inhibiting tic execution or by improving the ability to suppress tics) should also be investigated.

Limitations

There are several limitations of the present review. As already mentioned above, the most obvious limitation is that our results are mainly based on case reports and case series with a high risk of bias. In addition, not all individual data were available, and aggregate data had to be extracted for some studies. This was mitigated by weighting the data by sample size for statistical analysis. Regarding the subgroup analyses, the numbers of patients in each target group varied. Notably, the number of patients in the CM-Pf target group for the YBOCS subgroup analysis was very low. The meta-analysis for all targets combined included only six RCTs, with a high heterogeneity in terms of time frame, procedure, outcome measures and target selection. Considering that the effects of DBS continue to manifest up to more than 12 months after surgery, one could argue that the included RCTs are also generally too short. Next, when drawing conclusions, one should be aware that the included articles in the present systematic review represent a very heterogenous data pool. The significant effects might be influenced by other factors, such as patient selection, tic severity before surgery, age, sex, poor compliance, medication, placebo effect in open-label settings, or stimulation parameters. Moreover, the wide time range of the maximum follow-up is another limitation, that may influence the results systematically. Taking into account the increase in the effectiveness of DBS over time, it may be considered problematic to report aggregated follow-up scores that span more than six months. For global YGTSS scores, we were unable to further narrow down the time category T3 (>12 months), because of insufficient data. Therefore, no statistical analyses were reasonably possible to examine whether the beneficial effects ceased over time. For the future, the use of international registries might contribute as part of the solution for this problem (146). It would also have been worthwhile to examine whether the increase of clinical efficacy of DBS differs between the four targets. Unfortunately, this was also not possible due to insufficient data. Another limitation refers to the assessment of TS symptomatology. The diversity of symptoms is not reflected in mean scores, such as the global YGTSS or YBOCS score. Thus, the heterogeneity of tics and comorbid symptoms was not considered in the present

analysis. Moreover, to evaluate the effect of DBS on more of the heterogenous symptoms of TS, it would have been helpful to include additional psychiatric scales in the final analysis, including assessments of the premonitory urge (Premonitory Urge for Tic Scale - PUTS), and quality of life (Gilles de la Tourette Syndrome-Quality of Life Scale - GTS-QoL) (147, 148). However, these assessments were very rarely used in the included studies. Lastly, no side effects of DBS were reviewed in the present work. These limitations should be considered when planning and conducting future research, especially randomized controlled and double-blinded trials.

Conclusion

We conclude that DBS is a clinically effective treatment option for patients with treatment-refractory TS, with all targets showing comparable significant improvement rates. However, the present results suggest that reduction rates in tic symptoms may differ across targets up to 12 months after surgery. Importantly, it may take at least one year for the positive effects of DBS to fully develop, and therefore no conclusions can be drawn about potential differences in long-term clinical outcomes between targets. Future research might shift its focus away from identifying one appropriate target for DBS in TS and instead enable personalized and symptom-specific target selection. A first step in this direction might be the characterization of target- and symptom-specific networks modulated by DBS.

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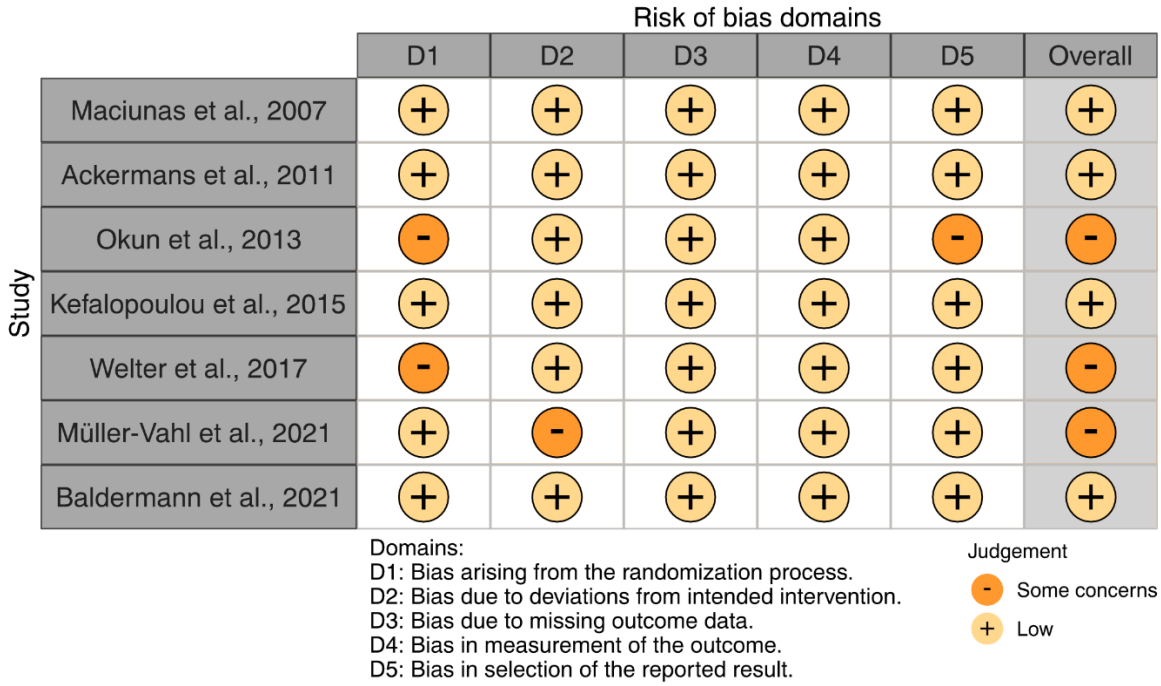
S**upplementary Material**



Supplemental Figure 1: Summary table of risk of bias domains in each RCT created with the risk of bias visualization (robvis) tool (149).

Supplement Materials 1: Search Terms

Database	**Search Syntax**
Pubmed	(("tourette syndrome"[MeSH Terms] OR ("tourette"[All Fields] AND "syndrome"[All Fields]) OR "tourette syndrome"[All Fields] OR ("tourette syndrome"[MeSH Terms] OR ("tourette"[All Fields] AND "syndrome"[All Fields]) OR "tourette syndrome"[All Fields] OR ("gilles"[All Fields] AND "de"[All Fields] AND "la"[All Fields] AND "tourette"[All Fields] AND "syndrome"[All Fields]) OR "gilles de la tourette syndrome"[All Fields]) OR ("tourette syndrome"[MeSH Terms] OR ("tourette"[All Fields] AND "syndrome"[All Fields]) OR "tourette syndrome"[All Fields] OR ("tourettes"[All Fields] AND "disorder"[All Fields]) OR "tourettes disorder"[All Fields]) OR ("tic disorders"[MeSH Terms] OR ("tic"[All Fields] AND "disorders"[All Fields]) OR "tic disorders"[All Fields] OR ("tic"[All Fields] AND "disorder"[All Fields]) OR "tic disorder"[All Fields])) AND ("deep brain stimulation"[MeSH Terms] OR ("deep"[All Fields] AND "brain"[All Fields] AND "stimulation"[All Fields]) OR "deep brain stimulation"[All Fields] OR "DBS"[All Fields])) AND (1999/1/1:2021/7/8[pdat])

3. General Discussion Section

3.1 Summary of Study Results

The two-sided objective of this dissertation was to investigate the underlying electrophysiological dynamics of TS and explore the therapeutic potential of DBS. Through these investigations, the overall aim was to enhance our understanding of the TS pathophysiology and applications of DBS, ultimately providing the directions for personalized stimulation-based treatment strategies.

The first study aimed to investigate electrophysiological correlates of cognitive processes that may play a role in the manifestation of tics in patients with TS (Wehmeyer et al., 2023). A cued task-switching paradigm combined with RIDE was employed to comprehensively examine distinct cognitive processes, including proactive control, perceptual binding, and perception-action binding. While cognitive processing at the behavioral level appears unchanged in the present patient group, notable differences in underlying neural dynamics have been observed. Specifically, cue-locked sustained parietal activity underlying proactive control processes, responsible for preparing cognitive resources in anticipation of a task switch signaled by the cue, remains unaltered in the present TS group, indicating intact proactive control processes in TS (Karayanidis & Jamadar, 2014; Nicholson et al., 2005; Travers & West, 2008). Furthermore, the target-locked parietal P3 in the S-cluster, reflecting pure perceptual binding processes influenced by interference from task set-target bindings, exhibited similar modulations in both groups, indicating unaltered perceptual binding in TS (Kopp et al., 2020). However, perception-action binding (i.e. task set-response binding) processes, reflected by the target-locked fronto-central N2 and parietal P3 in the C-cluster, were found to be modulated differently in the TS group. The C-cluster N2 modulation, presumably representing processes related to conflict resolution and response inhibition to overcome interference caused by task set-response bindings (Gajewski et al., 2010; Karayanidis et al., 2003; Karayanidis & Jamadar, 2014), was absent in the TS group. Additionally, the C-cluster P3 modulation, associated with context updating, presumably rebinding, and response selection to overcome interference caused by task set-response bindings (M. Kleimaker et al., 2020; Petruo et al., 2016; Takacs et al., 2020), exhibits an inverse pattern in the TS compared to the control group.

Collectively, this comprehensive investigation into the complex cognitive foundations of TS and their neurophysiological underpinnings strongly indicates that fronto-central and

parietal processes of perception-action binding are indeed altered in individuals with TS, while proactive control and pure perceptual binding processes appear to remain unaffected. These findings highlight the crucial interplay between perceptual processes and motor actions in TS, aligning with the emerging understanding of an abnormal interrelation between these processes contributing to tic occurrence in TS (Beste & Münchau, 2018).

The second study aimed to examine the effectiveness of DBS in TS and systematically compare the clinical effects of CM-Voi, CM-Pf, pvlGPi, and amGPi DBS through a systematic review and meta-analysis (Wehmeyer et al., 2021). This analysis encompassed data from 65 studies involving total of 376 patients. Overall, DBS in TS led to a significant tic improvement at the latest available follow-up, as assessed with the global Yale Global Tic Severity Scale (YGTSS). More specifically, around 70% of all patients experienced a tic reduction exceeding 50%. Notably, these improvements in tics were noticeable as early as six months post-surgery and continued to increase significantly for over a year. The results also indicated that general DBS yielded a similar significant reduction of secondary tic-related measures, as well as OCD and depressive symptoms improvement. Interestingly, when comparing tic improvement rates up to one year post-surgery across the four targets, DBS yielded significant tic improvement for all targets, albeit with notable differences across targets favoring pallidal DBS. Similarly, when comparing comorbid OCD symptom improvement rates, as assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS), at maximum follow-up across targets, pallidal stimulation resulted in greater improvement of comorbid OCD symptom. Furthermore, a meta-analysis of randomized controlled and double-blinded trials (RCTs) revealed that thalamic/pallidal DBS combined led to a significant reduction in tic severity when active compared to when inactive. However, this effect was not observed for thalamic targets alone, but for pallidal targets (Wehmeyer et al., 2021).

In summary, DBS constitutes a clinically effective therapeutic option for individuals with treatment-resistant TS. While each DBS target demonstrates substantial effectiveness, pallidal DBS stands out with the highest rates of improvement for both tics and comorbid OCD symptoms. This underscores the critical need to carefully tailor DBS target selection to the specific symptoms and unique characteristics of each patient.

3.2 The Long-Lasting Question of Impaired Volitional Cognitive Control in TS

The findings from Study 1 contribute to the existing body of research, adding to the inconclusive evidence regarding potential volitional cognitive control impairments in TS (Morand-Beaulieu et al., 2017). Notably, the present results of Study 1 indicate that proactive control remains intact in the studied patient group (Wehmeyer et al., 2023), contradicting the prevailing notion that tics may result from impaired inhibitory control (Ganos, Kahl, et al., 2014; Morand-Beaulieu et al., 2017). Considering the patients' capacity to suppress their tics, which implies that individuals with TS can exert control over their tics, it appears logical that proactive control remains intact in TS (Ueda et al., 2021). In fact, it has been proposed that the ongoing demand for tic suppression in patients with TS may result in heightened inhibitory motor control, extending to volitional cognitive control measures in laboratory settings (Ganos, Kuhn, et al., 2014; Jackson et al., 2007; Jackson et al., 2011; Mueller et al., 2006). An existing relationship between proactive control abilities and tic suppressibility would suggest that the level of proactive control is related to the patient's ability to suppress tics. Consequently, in a patient group with a generally low tic suppressibility, proactive control might be compromised. In this regard, the variability in findings across previous studies investigating volitional cognitive control in TS may, in part, be attributed to varying levels of tic suppressibility between the studied patient groups, which is often an potential uncontrolled confounding factor due to the absence of suitable measurements for assessing tic suppressibility. Collectively, the current results from Study 1, in line with the inconsistent findings in prior research, imply that volitional cognitive control impairments are not a fundamental feature in the pathophysiology of TS and are not directly linked to the mechanisms responsible for tic emergence. Instead, volitional control processes, both proactive and reactive, may be better understood as mechanisms associated with voluntary tic suppression.

3.3 Perception-Action Binding as a Potential Mechanism of Tic Generation in TS

When studying the neural processes underlying tics, it is essential to consider mechanisms associated with tic generation. One such mechanism proposed is reduced automatic control, as opposed to volitional control. According to this perspective, a constant stream of potential movement triggers from the environment continuously prompts actions, which are typically suppressed by automatic control processes beyond voluntary control (Rawji et al., 2020). While Rawji et al. (2020) indeed found normal proactive and reactive but impaired automatic control,

another study by Stenner et al. (2018) reported no differences in automatic control between patient with TS and healthy controls. However, a counterargument to this perspective is that individuals with TS often have a habit of unconsciously suppressing their tics, particularly in social situations, which has led to the suggestion that patients with TS may exert automatic chronic control over their tics (Brandt et al., 2017; Ueda et al., 2021). This notion aligns with the concept that tic suppression can be considered a learned behavior, which might occur automatically and involuntarily after years of tic suppression experience (Stenner et al., 2018; Ueda et al., 2021). Although remaining unclear, even if the automatic disinhibition model were valid, it would offer insights into only certain aspects of tic generation while not accounting for fundamental features of TS, such as PMU. Another potential mechanism involved in tic generation taking into account the PMU is the concept of perception-action binding (Beste & Münchau, 2018), which is supported by the current findings in Study 1 (Wehmeyer et al., 2023). Study 1 has revealed distinct neurophysiological changes in TS related to the perceptual-action binding rather than pure perceptual binding, emphasizing that especially bindings involving motor actions are affected in TS, which is in line with previous research (M. Kleimaker et al., 2020; Mielke et al., 2021; Petruo et al., 2016). Moreover, abnormal activity patterns associated with perception-action binding were evident in fronto-central and left-lateralized parietal areas (Wehmeyer et al., 2023). These results align with prior research that explicitly implicates the crucial role of a fronto-parietal network in perception-action binding, with the left inferior parietal cortex being specifically responsible for updating internal representations using sensory information to initiate appropriate actions, and the middle frontal gyrus for conflict resolution (M. Kleimaker et al., 2020; Opitz et al., 2020; Petruo et al., 2016; Weissbach et al., 2023). Although the precise nature of interaction between fronto-central and parietal regions remains uncertain, Study 1 underscores atypical neural dynamics within this fronto-parietal network underlying perception-action binding processes, consistent with fMRI research indicating abnormal resting-state connectivity patterns within the fronto-parietal network in TS (Church et al., 2009; Worbe et al., 2012).

In summary, the present research enhances our understanding of the neural processes underlying tics, specifically highlighting alterations in electrophysiological correlates of perception-action binding processes potentially related to tic generation, and identifying a fronto-parietal network that plays a critical role in these processes.

3.4 The Road to Personalized DBS in TS

While Study 2 recognizes the overall effectiveness of DBS for TS in reducing tic severity and alleviating comorbid symptoms, it also revealed that the clinical impact of DBS may vary depending on the specific target. Pallidal targets, in particular, exhibit superior therapeutic effects when compared to thalamic targets (Wehmeyer et al., 2021). Despite these valuable insights, the factors responsible for the differential target-specific effects remain elusive. Notably, the precise mechanism of action of target-specific DBS is, as of now, unknown. It is plausible that the different targets function as nodes within separate or interconnected networks, and modulation of these nodes may influence other nodes within the same network or affect the communication between network nodes (Neumann, 2022). To elaborate on this, the varying target-specific clinical effects might be attributed to the modulation of distinct networks, leading to the improvement of specific symptoms via certain functional mechanisms, although the exact nature of these mechanisms remains unknown (Wehmeyer et al., 2021). Given the unknown nature of the precise mechanism of action for target-specific DBS, and considering that all targets have demonstrated effectiveness in Study 2 (Wehmeyer et al., 2021)., there is currently no rationale for favoring one target over another. Importantly, it is improbable that a single appropriate DBS target, identified based on group-level results, can serve as a one-size-fits-all solution for TS, thereby accounting for the heterogenous phenotypes and comorbidities in TS (Hollunder et al., 2022). Hence, there is a compelling need for a personalized approach for DBS target selection, tailored to the patient's specific symptoms and characteristics.

A promising avenue for adopting a personalized approach is to select DBS targets within networks associated with specific symptoms, assuming that stimulating the local target influences the entire network (Hollunder et al., 2022; Horn & Fox, 2020). Consequently, stimulation of distinct networks may be necessary to address different symptoms and, theoretically, in cases where patients exhibit multiple symptoms that require modulation of various symptom-specific networks, multiple DBS targets may need to be considered (Horn & Fox, 2020). Embracing a prospective personalized approach would accommodate the heterogeneity and complexity of TS by targeting networks associated with various types of tics (i.e. motor vs. vocal, simple vs. complex), the PMU, and comorbid symptoms. This underscores the critical need for research to identify these symptom-specific networks in TS. In this regard, connectomic DBS holds great potential for guiding symptom-specific target selection by revealing the connectivity profiles of the target regions linked to specific symptom

improvement. This is achieved by correlating baseline connectivity profiles with clinical outcomes to identify optimal networks for maximum improvement, utilizing structural and functional connectivity data from advanced imaging techniques (Neumann et al., 2023). While connectomic DBS has already revealed distinct networks linked to tic improvement in previous TS research (Wehmeyer et al., 2021), the effectiveness of these networks depends on the precision of the clinical scales used for symptom assessment. For example, the commonly used YGTSS score quantifies overall tic severity, comprising various aspects of tics, including number, frequency, intensity, complexity, and interference of tics (Leckman et al., 1989). Consequently, a YGTSS change score and the associated connectivity network fail to provide detailed insights into the specific aspects of tics that have been improved or the precise functional mechanisms responsible for tic improvement (e.g., direct inhibition of tic generation or enhancement of tic suppressibility). This limitation significantly impedes our ability to comprehensively understand how DBS contributes to the symptom improvement, thereby hindering the effective refinement and optimization of DBS treatment.

Expanding upon this, by identifying the fundamental underlying mechanisms driving TS symptoms, DBS could precisely target and modulate network activity associated with these mechanisms. This precision holds the potential to significantly enhance symptom management by addressing the root causes of TS, thereby offering more efficient and precisely tailored treatments. Moreover, this precision is not limited to the initial target selection phase, but extends to subsequent stages, including the optimization of stimulation parameters and the implementation of closed-loop DBS. However, developing such a tailored approach for DBS in TS requires a comprehensive understanding of the underlying pathophysiological mechanisms of TS, which is currently lacking.

3.5 The Question of a Tic Biomarker

To enhance the precision of tailored DBS treatments, it is crucial to identify biomarkers within networks associated with TS mechanisms. Any accessible network node could potentially serve as target for various neuromodulation methods, DBS, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and vagus nerve stimulation (VNS). While the ideal approach would involve identifying comprehensive TS networks for flexible targeting, the current knowledge gap necessitates a focus on local neural markers associated with symptoms, which can potentially be modulated through stimulation-based treatment approaches. This section will primarily discuss potential biomarkers of the core TS symptoms,

tics and urges, for neuromodulation in general. However, it is vital to acknowledge that a comprehensive tailored approach should also consider comorbid symptoms. For simplicity, the general neural correlates of tics will be discussed without addressing the intricacies introduced by tic heterogeneity, which would further add to the complexity of this discussion. Also, this discussion emphasizes electrophysiological markers, given their capacity for real-time monitoring, a crucial aspect for capturing the rapid mechanisms underlying tics and facilitating precision in neuromodulation interventions, especially with regard to closed-loop systems.

What could serve as a potential marker for tics that neuromodulation interventions can target? In principle, tic generation is a complex process, likely driven by various interrelated functional mechanisms, each operating at different stages before the actual tic occurs. Some of these mechanisms may play a more direct role in tic generation than others. Theoretically, biomarkers within networks associated with these functional mechanisms at different stages could be candidates for targeted neuromodulation to halt the progression of tic development. Additionally, secondary control mechanisms that have the potential to interrupt the tic development process could also serve as viable targets for neuromodulation. In this context, potential neuromodulation targets may encompass accessible nodes within networks associated with (Figure 4):

i. The premonitory urge
ii. Perception-action binding
iii. Tic initiation
iv. Tic control

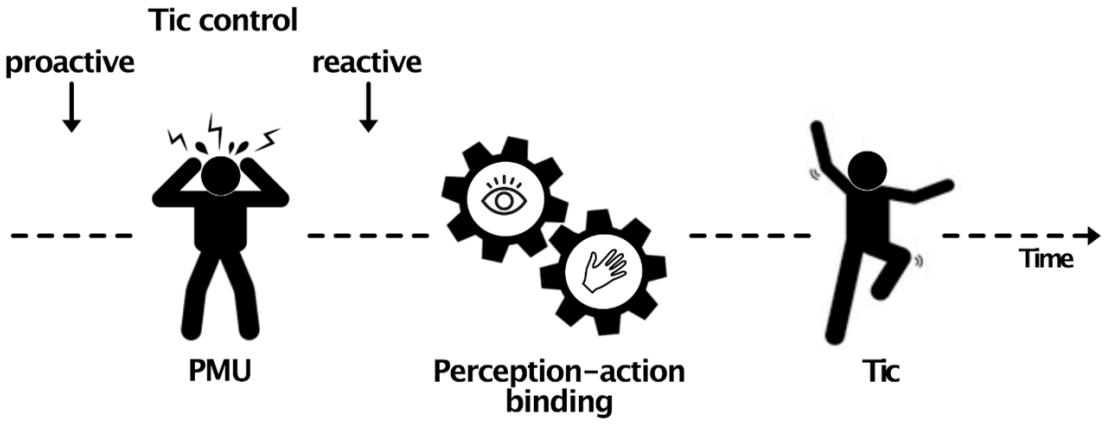


Figure 4: Functional mechanisms at different stages that could be potenital candidates for targeted neuromodulation to halt the progression of tic development: the premonitory urge (PMU), perception-action binding, tic initiation, and tic control (proactive or reactive).

3.5.1 The Premonitory Urge

The PMU typically precedes tics in TS and may play a significant role in initiating the tic development process (Cavanna et al., 2017). Moreover, the PMU itself presents an uncomfortable and distressing sensation, which may have a negative impact on the individual's quality of life (Crossley & Cavanna, 2013). Consequently, targeting the PMU through neuromodulation could impede the progression of tic development and alleviate urges. While there is currently a lack of electrophysiological studies on the PMU, neuroimaging research has implicated a network involving primary and secondary sensory cortices, the insula, ACC, and SMA in the generation of the PMU (Cavanna et al., 2017). However, these investigations have primarily focused on tic suppression states, assuming that urges intensify when tics are suppressed, or before compared to after tics, in accordance with the typical temporal pattern of urges increasing and decreasing around tics (Brandt et al., 2016). These approaches challenge the disentangling of PMU-related activation from other factors in fMRI studies. However, in fact, the characteristic temporal fluctuations of urges offer a great opportunity to effectively disentangle urges from potential confounding factors. This can be accomplished by identifying a neurophysiological correlate of the urge using real-time objective measurements of urge intensity combined with high temporal resolution electrophysiology techniques (Brandt et al., 2016). Future studies should aim to investigate the neurophysiological patterns of the PMU's temporal characteristics to uncover potential targets for stimulation-based interventions aimed at alleviating urges and preventing tics.

3.5.2 Perception-Action Binding

Building upon prior research and the findings of Study 1 (M. Kleimaker et al., 2020; Wehmeyer et al., 2023), perception-action binding processes, responsible for integrating the sensory PMU with subsequent motor tic responses, emerge as promising targets for stimulation-based treatments aimed at disrupting the process leading to tic generation. More specifically, targeting abnormal activity patterns associated with perception-action binding within the fronto-parietal network may be a valuable approach to resolve the abnormally strong connection between PMU and tics, ultimately preventing the occurrence of the tic. While modulating local activity in the left inferior parietal cortex could influence binding processes per se, modulating activity in the middle frontal gyrus may enhance mechanisms for

overcoming, such as inhibiting, these bindings (M. Kleimaker et al., 2020; Opitz et al., 2020; Wehmeyer et al., 2023).

Notably, the cued task-switching paradigm, a valuable tool for investigating various cognitive processes within a single experimental design and uncovering alterations in electrophysiological correlates related to perception-action binding, may not provide a pure measure of these bindings. No behavioral effects related to perception-action binding were observed in Study 1, potentially due to the concurrent activation of proactive control processes and top-down influence on binding (Wehmeyer et al., 2023). Nonetheless, the observed alterations in neurophysiological markers of perception-action binding in TS were consistent with findings from other studies (M. Kleimaker et al., 2020), indicating a level of consistency and reproducibility in these markers. However, more research is necessary to establish the validity and reliability of these markers.

3.5.3 Tic Initiation

At the final stage of preventing tic occurrence, neuromodulation approaches could target neural activity responsible for initiating tics. Previous research has examined electrophysiological correlates of tics in comparison to voluntary movements, focusing on beta oscillations (13–30 Hz) over the sensorimotor cortex before tic onset. Typically, beta power is suppressed before or during voluntary movements, indicating motor readiness (Jenkinson & Brown, 2011; Pfurtscheller & Lopes da Silva, 1999). While one study identified a beta suppression pattern before tic onset (Niccolai et al., 2019), another showed an absence of this suppression (Morera Maiquez et al., 2022). This suggests that tic initiation may involve more complex brain network processes extending beyond beta oscillations in the sensorimotor cortex, challenging the notion that tics are solely voluntary responses to urges (Rae et al., 2019).

Expanding on this, LFP studies comparing tic-related and voluntary movement-related thalamic activity changes in DBS-treated TS patients have consistently revealed a distinct, unrhythmic low-frequency increase (range: 2–15 Hz) after tic onset (Bour et al., 2015; Cagle et al., 2020; Marceglia et al., 2021; Molina et al., 2018; Shute et al., 2016). Based on this feature, initial research has demonstrated the feasibility, safety, and comparable effectiveness of a closed-loop DBS approach in comparison to continuous DBS (Cagle et al., 2022). Importantly, this biomarker emerges after tic onset, rendering stimulation in response to this feedback signal too late to prevent the initial tic. However, the evident clinical tic improvement following adaptive DBS targeting this feature might be related to its effectiveness in preventing

subsequent tics, given the frequent occurrence of tics in sequences. Nonetheless, it remains preferable to identify a biomarker associated with the actual mechanism responsible for initiating tics before their onset. Interestingly, a recent study combing LFP and EEG recordings indicated a significant reduction in functional thalamo-frontal alpha (8-15 Hz) connectivity just before tic onset, suggesting a direct relationship with tic occurrence (Wehmeyer et al., in preparation). This finding underscores the significance of investigating dynamic network connectivity patterns as potential biomarkers, thereby informing future research aimed at identifying electrophysiological markers, particularly for closed-loop DBS in TS.

3.5.4 Tic Control

Beyond the functional mechanisms contributing to tic generation, neuromodulation approaches can target secondary mechanisms that enhance tic control, specifically voluntary tic suppression. Prior studies, comparing resting and tic suppression states, have identified a network associated with voluntary tic suppression, encompassing sensorimotor cortices, the inferior frontal cortex, and the ACC, with communication occurring within the alpha frequency band (Ganos, Kahl, et al., 2014; Morand-Beaulieu et al., 2023; Serrien et al., 2005; van der Salm et al., 2018). Within the framework distinguishing between proactive and reactive control, voluntary tic suppression can involve both reactive (e.g., suppressing tics as a direct response to the PMU) and proactive elements (e.g., preparing the system to be ready to suppress anticipated tics) (Rawji et al., 2020).

Individuals with TS may employ proactive tic control strategies in specific trigger situations or during goal-directed tasks to prevent tics from interfering with their actions (Ganos, Kuhn, et al., 2014; Zea Vera et al., 2022). Consequently, proactive tic control is more a tonic rather than acute process (Rawji et al., 2020). Study 1 revealed sustained parietal activity associated with readiness for motor action control, likely linked to attentional focus reallocation (Wehmeyer et al., 2023). While consistent evidence of impaired proactive control is lacking, the variability in findings across previous studies investigating proactive cognitive control in TS may suggest the possibility of impaired proactive control in individual patients, potentially linked to reduced tic suppressibility (Morand-Beaulieu et al., 2017; Wehmeyer et al., 2023). Targeting proactive control mechanisms to enhance tic suppressibility in these individual patients could be beneficial. Interestingly, as mentioned before, proactive control processes may interact with binding processes, and the top-down influence of sustained proactive control

may lead to reduced activation of perception-action binding (Dutzi & Hommel, 2009; Frings et al., 2020; Hommel, 2022; Wehmeyer et al., 2023).

Furthermore, individuals with TS may employ reactive tic control strategies in response to the PMU, representing an acute process (Ganos, Kuhn, et al., 2014; Rawji et al., 2020; Zea Vera et al., 2022). Notably, reactive tic suppression may also interact with binding processes by resolving perception-action bindings. Using real-time objective measurements of urge intensity, Brandt et al. (2016) demonstrated changes in urge distribution under tic suppression, indicating that tic suppression can disentangle urges from tics, potentially breaking the strong interrelation between the two. In this context, the modulated frontal activity by perception-action binding observed in Study 1, related to conflict resolution and response inhibition to overcome interference caused by bindings, could represent such a reactive control process (Gajewski et al., 2010; Karayanidis et al., 2003; Karayanidis & Jamadar, 2014).

Beyond that, tic control may persist even when patients are not actively attempting to suppress their tics, as it often occurs automatically and involuntarily, especially in social situations (Brandt et al., 2017; Ueda et al., 2021). Consequently, neuromodulation approaches could be directed towards targeting the mechanisms of automatic tic control. In support of this idea, recent research combining LFP and EEG recordings has demonstrated that increased functional thalamo-frontal alpha (8-15 Hz) connectivity at rest is associated with reduced tic symptom severity (Wehmeyer et al., in preparation). Although the specific mechanisms underpinning this observed association remain speculative, it has been hypothesized, based on the involvement of frontal regions, that heightened thalamo-frontal connectivity could potentially enhance chronic tic control. This hypothesis finds support in prior research linking fronto-striatal hyperconnectivity to chronic tic control (Brandt et al., 2017). It has also been postulated that both voluntary and automatic tic control involve top-down control mechanisms originating from frontal to subcortical regions, potentially normalizing abnormal activity within CBGTC circuits responsible for tics (Aron et al., 2003; Sumner et al., 2007; Ueda et al., 2021). While the precise mechanisms governing thalamo-frontal connectivity in the alpha band remain unclear, its correlation with tic symptom severity suggests its potential as a target for stimulation-based treatments in patients with TS. In accordance with this, a neuroimaging study has identified a DBS-dependent functional connectivity network linking the thalamus to the medial frontal cortex that strongly correlated with tic improvement (Baldermann et al., 2022).

In sum, understanding the interplay of proactive, reactive, and automatic control mechanisms in the context of tic suppression and their possible interaction with perception-

action binding offers valuable insights into potential targets and approaches for neuromodulation therapies in individuals with TS.

3.6 Future Directions

In summary, these potential biomarkers and mechanisms provide valuable insights into the various facets of tic development and control, presenting promising avenues for targeted neuromodulation. These insights are not only useful for optimized target selection but also for fine-tuning stimulation parameters and the development of closed-loop systems. Importantly, the effectiveness of neuromodulation, when targeting the mechanisms discussed, depends on the brain's state during stimulation. For mechanisms related to tic generation, the brain must be in a state where urges or tics are occurring, rendering markers of tic generation less useful during resting states. In this regard, these mechanisms underlying tic generation might lay the foundation for developing a closed-loop system, operating based on the brain's specific state. Conversely, mechanisms related to proactive and automatic control represent more chronic states that can potentially be influenced by neuromodulation during resting-state. Essentially, these states of tic control do not provide a specific timed marker allowing for closed-loop stimulation. In contrast, reactive control in response to interference caused by perception-action binding represents an acute process, enabling marker detection and subsequent modulation. Importantly, when selecting targets, it is crucial to ensure that the to be modulated network includes the nodes associated with these markers. Subsequently, in a closed-loop system, these markers can serve as feedback, guiding stimulation in response to them.

Developing such a tailored approach for neuromodulation in TS requires a much more comprehensive understanding of the underlying pathophysiological mechanisms, which is currently lacking. The mechanisms discussed in this work provide an initial step into this direction and offer the potential for flexible personalized targeting based on individual characteristics. This approach can accommodate the heterogeneity of TS and also the symptom fluctuations over time by individually targeting the specific mechanisms suitable for each patient.

It is also essential to underscore the significance of ongoing research and exploration aimed at deepening our understanding of these mechanisms and potentially identifying new ones. Specifically, future research should be aimed at validating and enhancing the reliability of these markers, as well as exploring dynamic network connectivity patterns as potential biomarkers by, for example, combining LFP and scalp recordings. In addition, a

comprehensive understanding of the intricate interplay between proactive, reactive, and automatic control mechanisms within the framework of tic suppression, and their potential interaction with perception-action binding, could be beneficial to understand how tic control mechanisms can be optimally enhanced. Moreover, once there are validated and reliable biomarkers, the next step would be to conduct studies or experiments to assess how neuromodulation affects these biomarkers and eventually can lead to clinical symptom improvements in TS.

3.7 Limitations

While this dissertation provides valuable insights into various aspects of TS and the potential therapeutic applications of DBS, it is important to acknowledge several limitations that should be considered when interpreting the findings.

First, TS is a highly heterogeneous condition characterized by diverse variations in symptom severity, symptom presentation, and the presence of comorbidities among affected individuals. The studies and analyses presented in this dissertation may not capture the full spectrum of TS manifestations. Therefore, generalizing the group-level findings to the general TS population should be done with caution, as the underlying mechanisms and the efficacy of treatments may differ among patients. The limitations of group-level analyses extend further when seeking a real-time biomarker for guiding adaptive DBS. It is imperative that such a biomarker not only emerges when data are averaged across numerous trials and patients but is also robust and reliable for real-time detection. Hence, future investigations should emphasize the application of single-subject analyses to account for the considerable variability and nuances that characterize TS in individual patients.

Second, while this dissertation primarily addresses cognitive and neurophysiological aspects of TS, it does not encompass other significant factors such as genetics, environment, and social influences. It is crucial to recognize that these factors interact in a complex manner, necessitating interdisciplinary research for a more comprehensive understanding. Additionally, the controlled laboratory setting, which may represent a socially uncomfortable environment for patients, may introduce unaccounted confounding factors that could impact research outcomes.

A third noteworthy limitation, primarily in the first part of this dissertation, was the constraint imposed by relatively small sample sizes. Larger and more diverse samples would have provided more robust findings and also allowed for subgroup-analyses to account for the

diversity within the TS population. However, it is important to note that the challenge of working with limited sample sizes is a common issue encountered in research involving neuropsychiatric patients, stemming from practical and ethical considerations.

Another challenge in conducting research with neuropsychiatric patients pertains to the assessment of psychiatric and psychological symptoms. Although several validated assessment tools for TS symptoms exist, depending solely on their primary measures may not adequately encompass the full spectrum of symptom heterogeneity. This consideration is particularly important when evaluating the impact of DBS on tic symptoms. Furthermore, given the ongoing advancement of our understanding of TS pathophysiology, the assessment of specific phenomena like the urge or tic suppressibility is still developing or incomplete, which adds complexity to the research.

Furthermore, although the second part of the dissertation offers valuable insights into the effectiveness of target-specific DBS in TS, it is crucial to acknowledge that the selection of the optimal DBS target remains a multifaceted challenge. This work does not present specific guidelines for the precise selection of the most suitable DBS target for individual patients, as this complex decision necessitates further research and clinical expertise. The current dissertation addresses this issue by emphasizing the importance of personalized DBS targeting and extensively discussing potential pathways to achieving this level of personalization.

Importantly, while DBS is a focus of this dissertation, it is essential to recognize that there are alternative therapies for TS, including behavioral interventions, pharmacotherapy, and alternative (non-invasive) stimulation-based treatment approaches. These treatments, although beyond the scope of this work, play a significant role in the management of TS and should be considered in a comprehensive treatment approach.

Moreover, when discussing the potential for advanced neuromodulation methods, such as closed-loop systems, ethical and biological factors must be taken into account. The development of these advanced treatment methods involves regulatory, ethical, and safety considerations that extend beyond the scope of this research.

In conclusion, this dissertation represents an important step in advancing our knowledge of TS and the potential of DBS as a therapeutic option. However, the aforementioned limitations should be acknowledged, and further research is needed to address these constraints and to provide a more comprehensive and personalized approach to TS treatment.

3.8 Conclusion

This dissertation has conducted a comprehensive exploration of TS and its potential therapeutic applications, with a primary focus on DBS. The overarching goal was to enhance our understanding of the TS pathophysiology and explore potential avenues for personalized stimulation-based treatment strategies.

One key objective has been to advance our understanding of the complex cognitive underpinnings of TS and their corresponding neurophysiological manifestations. Through a comprehensive electrophysiological investigation of various cognitive processes potentially linked to tic occurrence, including volitional cognitive control and binding, this research offered a holistic insight into the complex cognitive foundations of TS and their neurophysiological correlates. The findings underscore the alteration of neurophysiological perception-action binding processes in TS, while proactive control and pure perceptual binding processes remain unaffected. These results highlight the essential interplay between perceptual processes (i.e. PMU) and motor actions (i.e. tics) in the context of TS, aligning with the emerging understanding of an abnormal interrelation between these processes contributing to tic expression in TS.

Another key objective was to deepen our understanding of the clinical potential of DBS for individuals with treatment-refractory TS. Through a systematic review and meta-analysis, the efficacy of DBS in TS across various targets, including the CM-Voi, CM-Pf, pvlGPi, and amGPi, was systematically assessed. The findings underscore DBS as a clinically effective treatment option for treatment-resistant TS, with pallidal DBS showing the highest improvement rates. However, these results do not provide a rationale for favoring one target over another. Instead, they emphasize that no single DBS target can account for the heterogeneous phenotypes and comorbidities in TS. Therefore, personalized DBS target selection tailored to each patient's specific symptoms and characteristics is essential.

Achieving this personalized precision approach requires a deeper understanding of biomarkers related to the underlying neurophysiological mechanisms driving tics in TS. Potential biomarkers for targeted neuromodulation can be altered neural mechanisms underlying urges, perception-action binding, tic initiation, or tic control. However, the mechanisms and potential markers discussed require further validation and research. Developing a comprehensive understanding of the neural mechanisms in TS and their interactions is essential to optimizing targeted neuromodulation treatments for TS.

In conclusion, this work highlights a significant step towards a better understanding of the underlying neural mechanisms of TS and exploiting the potential of DBS. It has illuminated the path towards personalized stimulation-based treatment strategies, underlining the need for further research. Recognizing the complexity and heterogeneity of TS, this inspires a deeper commitment to interdisciplinary research and personalized interventions, ultimately improving the well-being of individuals with TS.

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5. Erklärung zum geleisteten Beitrag zu den Publikationen

Hiermit versichere ich, dass ich den wesentlichen Beitrag zu den Erstautor-Publikationen geleistet habe, wie im Folgenden näher beschrieben:

Die erste Publikation mit dem Titel "Electrophysiological Correlates of Proactive Control and Binding Processes during Task Switching in Tourette Syndrome" entstand im Rahmen des Projekts "Charakterisierung von Handlungsregulationsdefiziten beim Tourette-Syndrom und deren Modulierbarkeit durch Tiefe Hirnstimulation (TOSHI)." Das Studiendesign wurde von Herrn Prof. Dr. Jens Kuhn, Dr. Thomas Schüller und Dr. Canan Schüller (damals Peisker) entwickelt. Die Erhebung der elektrophysiologischen und klinischen Daten erfolgte sowohl durch Dr. Thomas Schüller und Dr. Canan Schüller als auch durch mich, wobei ich maßgeblich die EEG-Messungen zur Datenerhebung geplant habe und unter der Aufsicht von Dr. Thomas Schüller durchgeführt habe. Die Konzeption der Publikation und das Design der Datenanalyse erfolgte durch mich, wobei ich auf die Expertise der Koautoren zurückgriff. Die Daten wurden eigenständig von mir analysiert, evaluiert und interpretiert. Ebenso habe ich das Manuskript sowie die Abbildungen und Tabellen eigenständig erstellt. Den Revisionsprozess habe ich ebenfalls eigenständig durchlaufen. Die Koautoren standen mir während des gesamten Prozesses für Supervision und Unterstützung bei Fragen zur Verfügung und unterstützen mich bei der Editierung des Manuskripts.

Für die zweite Publikation mit dem Titel "Target-Specific Effects of Deep Brain Stimulation for Tourette Syndrome: A Systematic Review and Meta-Analysis" habe ich das Konzept der Publikation und das Design der Datenanalyse eigenständig entwickelt, wobei ich auf die Expertise der Mitautoren zurückgriff. Die Daten wurden von mir erhoben, analysiert, evaluiert und interpretiert. Das Manuskript, einschließlich der Abbildungen und Tabellen, wurde von mir eigenständig erstellt, mit Ausnahme einer Abbildung, für deren Erstellung eine spezielle Software erforderlich war, wobei mir Dr. Petra Heiden unterstützend zur Seite stand. Ebenso habe ich den Revisionsprozess eigenständig durchgeführt. Die Mitautoren haben mich im gesamten Prozess durch Supervision, Beantwortung von Fragen und Unterstützung bei der Editierung des Manuskripts unterstützt.

18.06.2024	Laura Wehmeyer
Datum	Unterschrift

6. Eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen - einschließlich Tabellen, Karten und Abbildungen -, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Priv.-Doz. Dr. Pablo Andrade betreut worden.

Darüber hinaus erkläre ich hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten der Universität zu Köln gelesen und sie bei der Durchführung der Dissertation beachtet habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Übersicht der Publikationen:

Wehmeyer, L., Schueller, C. B., Gruendler, T. O., Huys, D., Kuhn, J., Ullsperger, M., ... & Schueller, T. (2023). Electrophysiological correlates of proactive control and binding processes during task switching in Tourette syndrome. *Eneuro*, *10*(4). doi: 10.1523/ENEURO.0279-22.2023

Wehmeyer, L., Schueller, T., Kiess, J., Heiden, P., Visser-Vandewalle, V., Baldermann, J. C., & Andrade, P. (2021). Target-specific effects of Deep Brain Stimulation for Tourette syndrome: A systematic review and meta-analysis. *Front. Neurol.* 12:769275. doi:10.3389/fneur.2021.769275

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem IPHS-Promotionsausschuss unverzüglich mitzuteilen.

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