Toward Personalized Medicine in Connectomic Deep Brain Stimulation

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List of abbreviations

ALIC	Anterior Limb of the Internal Capsule
BOLD	Blood Oxygenation Level Dependent
DBS	Deep Brain Stimulation
dMRI	diffusion-weighted Magnetic Resonance Imaging
DRT	Dentato-Rubro-Thalamic tract
ET	Essential Tremor
GPi	internal pallidum (Globus Pallidus internus)
MDD	Major Depressive Disorder
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal Cortex
PD	Parkinson's Disease
RDoC	Research Domain Criteria
rs-fMRI	resting state-functional Magnetic Resonance Imaging
STN	Subthalamic Nucleus
SCC	Subgenual Cingulate Cortex
UF	Uncinate Fasciculus
VTA	Volume of Tissue Activated

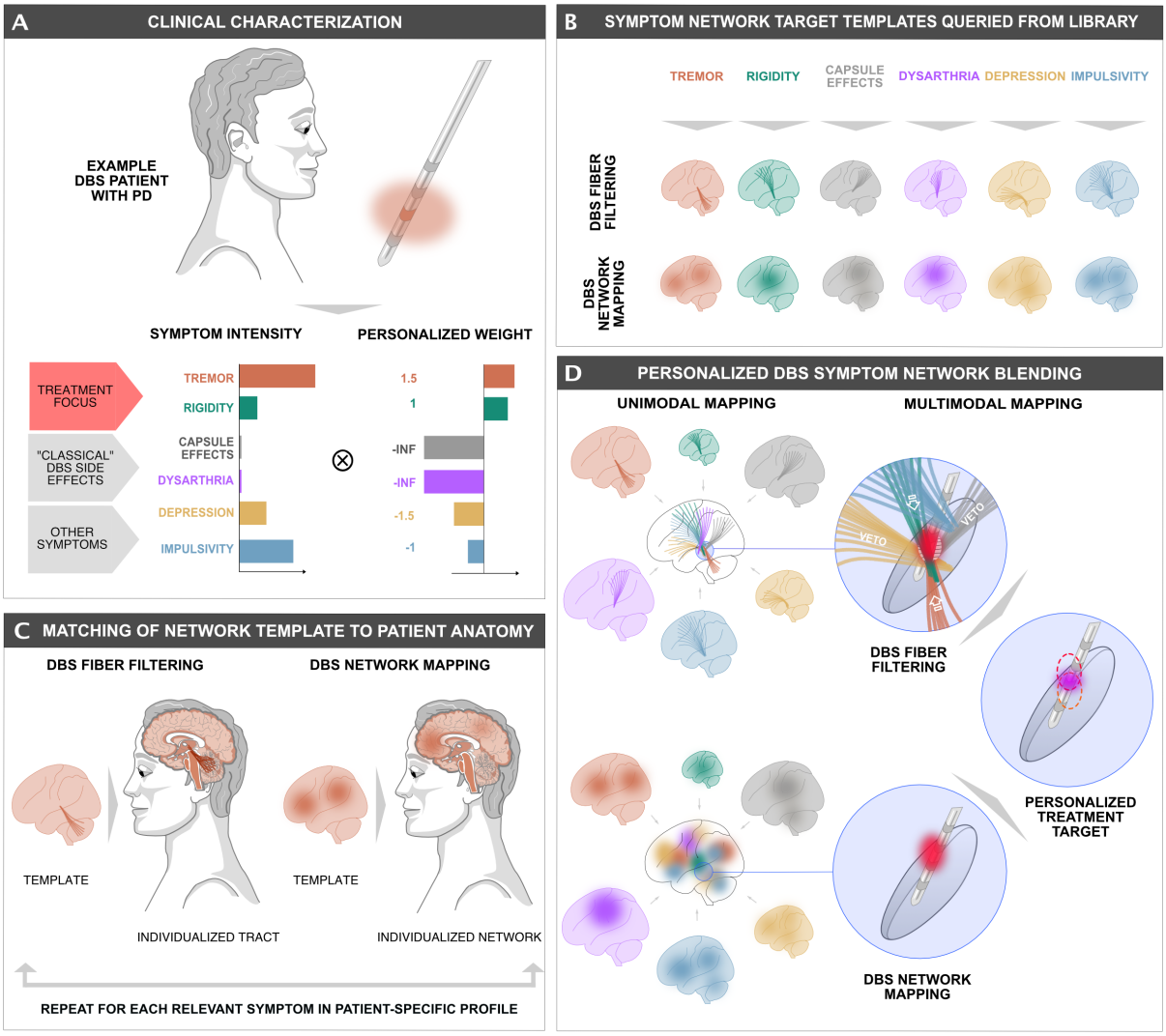
Abstract

At the group-level, deep brain stimulation leads to significant therapeutic benefit in a multitude of neurological and neuropsychiatric disorders. At the single-patient level, however, symptoms may sometimes persist despite “optimal” electrode placement at established treatment coordinates. This may be partly explained by limitations of disease-centric strategies that are unable to account for *heterogeneous* phenotypes and comorbidities observed in clinical practice. Instead, tailoring electrode placement and programming to individual patients’ symptom profiles may increase the fraction of top-responding patients. Here, we propose a three-step, circuit-based framework with the aim of developing patient-specific treatment targets that address the unique symptom constellation prevalent in each patient. First, we describe how a *symptom network target library* could be established by mapping beneficial or undesirable DBS effects to distinct circuits based on (retrospective) group-level data. Second, we suggest ways of matching the resulting symptom networks to circuits defined in the individual patient (*template matching*). Third, we introduce *network blending* as a strategy to calculate optimal stimulation targets and parameters by selecting and weighting a set of symptom-specific networks based on the symptom profile and subjective priorities of the individual patient. We integrate the approach with published literature and conclude by discussing limitations and future challenges.

Keywords

Circuitopathies, connectomics, deep brain stimulation (DBS), neuromodulation, personalized medicine, Research Domain Criteria.

Graphical abstract



1. Introduction

The advent of deep brain stimulation (DBS) has revolutionized neurological therapies and provided a unique window into the pathophysiology of neurocircuit dysfunction (Gardner, 2013; Priori, 2015). Along with technological and methodological advances the field has paved the path to over 200.000 DBS surgeries across a broad spectrum of brain disorders (Vedam-Mai et al., 2021). Apart from U.S. Food and Drug Administration approvals for Parkinson's disease (PD), essential tremor (ET), and epilepsy, DBS has received humanitarian device exemption for dystonia and obsessive-compulsive disorder (OCD) (Lee et al., 2019). Among the many investigational applications, examples are intractable major depressive disorder (MDD) (Dougherty et al., 2015; Holtzheimer et al., 2017; Mayberg et al., 2005), Alzheimer's disease (Kuhn et al., 2015; Laxton et al., 2010), chronic pain syndromes (Farrell et al., 2018), schizophrenia (Corripio et al., 2020; Wang et al., 2020), and minimally conscious states (Chudy et al., 2018; Yamamoto et al., 2005).

While DBS has reached standard-of-care status in various movement disorders (Fasano et al., 2015; Limousin and Foltynie, 2019; Moro et al., 2017), outcome variability is more pronounced in the neuropsychiatric domain (Alonso et al., 2015; Sullivan et al., 2021; Zhou et al., 2018). Notwithstanding the underlying pathophysiological correlate, response to DBS is dictated by a multitude of factors. These include differences in preoperative targeting strategies (*across* – but also *within* – surgical target sites), intraoperative electrode placement, stimulation contact and parameter selection, placebo effects, side-effects, or clinical and demographic patient characteristics (Limousin and Foltynie, 2019; Pilitsis et al., 2008). Even in established indications, however, symptom relief can remain absent for a fraction of treated patients despite accurate electrode placement (Okun et al., 2005; Pauls et al., 2017).

This latter observation has raised concerns that strategies developed for the "average" patient and their cardinal symptomatology could, in fact, obscure clinically meaningful variability of DBS effects onto the full symptom spectrum at the individual-patient level (Allawala et al., 2021; Figee and Mayberg, 2021). Indeed, both current DBS research and clinical practice predominantly rely on conditional diagnoses for pooling patients into clusters

for which best-practice neuromodulation strategies are continuously developed and revised. In view of symptomatic and pathophysiological *heterogeneity* within disorders (Marquand et al., 2016) along with cross-diagnostic *comorbidity* (Husain, 2017; Merikangas et al., 2015; Plana-Ripoll et al., 2019), the tendency toward a disease-centric "one-fits-all" approach may, however, limit personalized precision medicine in DBS (Casey et al., 2013; Cuthbert and Insel, 2013). Notably, even established diagnoses such as PD present with varying clinical phenotypes and the unity of a common pathology is increasingly being questioned (Fearon et al., 2021; Mestre et al., 2021). Moreover, with DBS optimization strategies often focusing on a cardinal set of symptoms for a given disorder, secondary symptomatology may become unmasked and undermine full recovery. For instance, PD patients often benefit from DBS to the subthalamic nucleus (STN) or internal pallidum (GPi) in terms of improved tremor, bradykinesia, rigidity, or motor fluctuations. Instead, symptoms pertaining to speech, affect, cognition – and even to the full range of motor features (such as freezing of gait) – may persist or even deteriorate following surgery (Rodriguez-Oroz et al., 2012).

By contrast, an interventional framework of higher adaptability to phenotypical heterogeneity could target an individual's biosignature (or *biotype*) in more granular fashion to enable reliable predictions of single-patient outcome within a comprehensive symptom range (Fernandes et al., 2017; Perlis, 2011; Strimbu and Tavel, 2010). Neuroimaging-based markers have shown particular clinical utility in treatment selection for individuals (Barcia et al., 2019; Drysdale et al., 2017; Dunlop et al., 2017; Kelley et al., 2021; Korgaonkar et al., 2015; McGrath et al., 2013). To define suitable neuroimaging biomarkers for personalized DBS it is worth closely examining its assumed mechanisms of action. DBS emits weak high-frequency pulses of electrical current via electrodes surgically implanted into subcortical white or grey matter targets (Jakobs et al., 2019). Increasingly, researchers focus on widespread DBS network effects above and beyond the focal target level itself (Alhourani et al., 2015; Ashkan et al., 2017; Horn and Fox, 2020; Lozano and Lipsman, 2013). Subsequently, the degree of modulation of specific networks has allowed to forecast symptom improvements across DBS cohorts, centers and disorders (Horn et al., 2019b, 2017; Li et al., 2021, 2020; Okromelidze et

al., 2020; Sweet et al., 2020). Establishing a comprehensive library (or atlas) of networks that, when modulated, clearly associate with distinct symptoms thus represents a valuable opportunity for personalized neuromodulation.

This rationale aligns with the agenda of the Research Domain Criteria (RDoC) initiative of the U.S. National Institute of Mental Health, which sees the future of precision medicine in treating neurological and neuropsychiatric conditions as *"disorders of the human connectome"* (or *circuitopathies*) (Gordon, 2016; Insel et al., 2010). The RDoC framework assumes that observable behavior along dimensional symptom axes would map onto distinct circuit dysfunctions (Cuthbert, 2014; Cuthbert and Insel, 2013; Insel, 2014). The latter may be altered in functionally selective ways by means of neuromodulation at any given network node (Crocker et al., 2013; Fox et al., 2014; Horn and Fox, 2020; Insel et al., 2010; Shephard et al., 2021). Going forward, we will use the term of *"symptom network"* to describe a specific network associated with a particular symptom cluster (introduced as *"symptomatotopy"* by Lozano and Lipsman (2013)). When referencing the impact of neuromodulation onto these networks, we will refer to *"symptom network targets".*

Individual re-combinations and degrees of importance of these symptom networks could explain phenotypical variability across patients. Beyond PD, symptom networks have been defined, for instance, in anxiety and MDD (Drysdale et al., 2017; Liang et al., 2020; Price et al., 2017; Wager and Woo, 2017; Williams, 2017), OCD (Harrison et al., 2013; Mataix-Cols et al., 2004; Thorsen et al., 2018), or psychotic disorders (Clementz et al., 2016; Ivleva et al., 2017) – some of which, however, failed to replicate (Dinga et al., 2019). At the same time, symptom networks could be *shared across* disorders along dimensional symptom axes (Husain, 2017). Compulsivity, reward processing, or inhibition are examples of functional dimensions which may each rely on uniform network underpinnings but contribute to the clinical presentations of *different* disorders (Gillan et al., 2017, 2016; Lansdall et al., 2017; Nusslock and Alloy, 2017; Robbins et al., 2019; van den Heuvel et al., 2016; Whitton et al., 2015; Yücel et al., 2019). Tailoring DBS to a *combination* or *blend* of symptom networks could thus augment disease-specific electrode implantation and programming strategies through added levels of

precision and facilitate improvement in unique phenotypes (Figee and Mayberg, 2021; Horn and Fox, 2020). This strategy also links with recent developments in DBS technology – such as directional leads with an option for independent stimulation contact selection – which invite a more modular approach to treating symptom clusters.

Building on concepts like these, here, we intend to formalize an emerging DBS personalization framework by multidimensional symptom profiling via connectomics as grounds for future development. Our manuscript should be seen as a *blueprint* or whitepaper which comprises several scientifically established aspects but also others that remain to be worked out. The proposed approach consists of three consecutive steps which will structure this manuscript, including i) creating group-level *symptom network target libraries*, ii) translating these network targets into patient space based on unique connectivity profiles *(template matching)*, and iii) selecting and weighting individualized networks according to the symptom spectrum of specific patients to synthesize personalized DBS targets *(network blending)*. Ultimately, the framework aims to refine surgical planning (i.e., electrode placement *within* established targets) and postoperative stimulation parameter programming to maximize DBS outcome while avoiding undesirable side-effects.

2. Toward a library of symptom networks

2.1. "Bottom-up" definition of symptom networks

Before addressing our main aim to empirically define a *symptom network target library* using neuromodulation, we touch upon other ways of matching brain networks to corresponding symptoms. Attributing function to specific circuits is a fundamental goal of neuroscience and has been pursued for centuries (Eickhoff et al., 2018).

A classic example of clustering brain function has been to segregate striatal loops and their parallel – but cross-communicating (Aoki et al., 2019; Guthrie et al., 2013; Kolomiets et al., 2001) – interconnections between cortex, basal ganglia, thalamus, and brainstem (Alexander et al., 1986; Alexander and Crutcher, 1990). These cortico-basal ganglia-thalamo-cortical loops have fundamentally defined treatment concepts of brain disorders by their preference to process blends of *sensorimotor*, *limbic,* or *associative* information (**Fig. 1A**). Domain-specific *"plus"* or *"minus"* symptoms are seen as consequences of dysfunction of respective loops. Namely, authors established parallels between motor *"plus"* symptoms such as dyskinesia (motor) with premature responding (associative) or mania/impulsivity (limbic) as results of hyperfunction or "overmodulation (Volkmann et al., 2010). Similarly, on the *"minus"* side, akinesia (motor) was set into parallel with reduced psychomotor speed (associative), or depression/apathy (limbic) following hypofunction or "undermodulation" (**Fig. 1B)**.

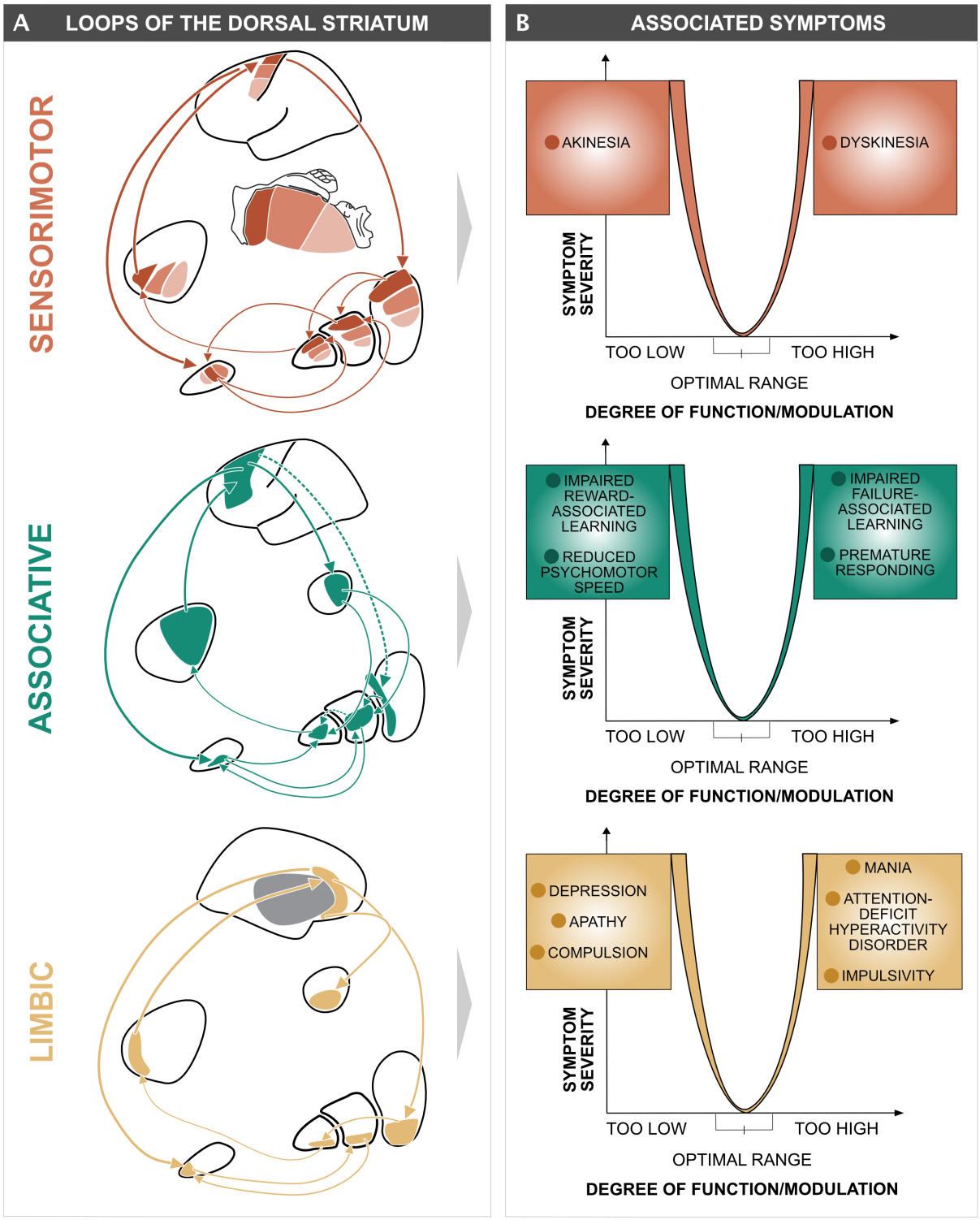


Fig. 1: Classical three-partite model of cortico-striatal loops. **(A)** The segregation into functionally selective cortico-basal-ganglia-thalamocortical loops initially proposed by Alexander et al. (1986) is schematically depicted. **(B)** Each loop is associated with corresponding *"plus"* and *"minus"* symptoms as inspired by Volkmann et al. (2010). Symptoms are assumed to be induced through (pathological) hyper- or hypofunction or "over- or undermodulation" via neuromodulatory approaches such as deep brain stimulation.

Further extending this concept of parallel striatal loops, Swanson proposed to generalize the functional description of “striatum” and “pallidum” to (all) remaining brain nuclei, which – based on their connections, neurotransmitter types and embryological development – would implicate network components with “striatal” or “pallidal” functional roles beyond the one involving the classical dorsal/ventral striatum (Swanson, 2003, 2000). Across all cortical loops, these roles would involve a cascading projection of excitation, inhibition, and disinhibition (**Fig. 2**). Following this logic, Swanson identified several circuits, each of which features a cortical region and regions functionally resembling a “striatum” and a “pallidum”. The hippocampo-septo-hypothalamic loop, for instance, comprises hippocampal cortical sites that exert excitatory effects on the lateral septal complex (“striatum”), which in turn inhibits the medial septal nucleus and nucleus of the diagonal band (“pallidum”). Since septal nucleus and diagonal band feature inhibitory projections, the net effect exerted by both structures would yield disinhibition, similarly to the cortico-striato-pallidal loop well defined in the dorsal striatum.

Once fully characterized, this framework could serve as a “bottom up” library of dedicated functional networks in patients undergoing DBS to guide the alteration of distinct symptoms (**Fig. 2)**. Conceivably, *sub*domains of proposed loops could be impacted in *multiple* ways, leading to different symptoms (e.g., tremor, bradykinesia, and dyskinesia as subnetworks of the dorsal striatum motor loop).

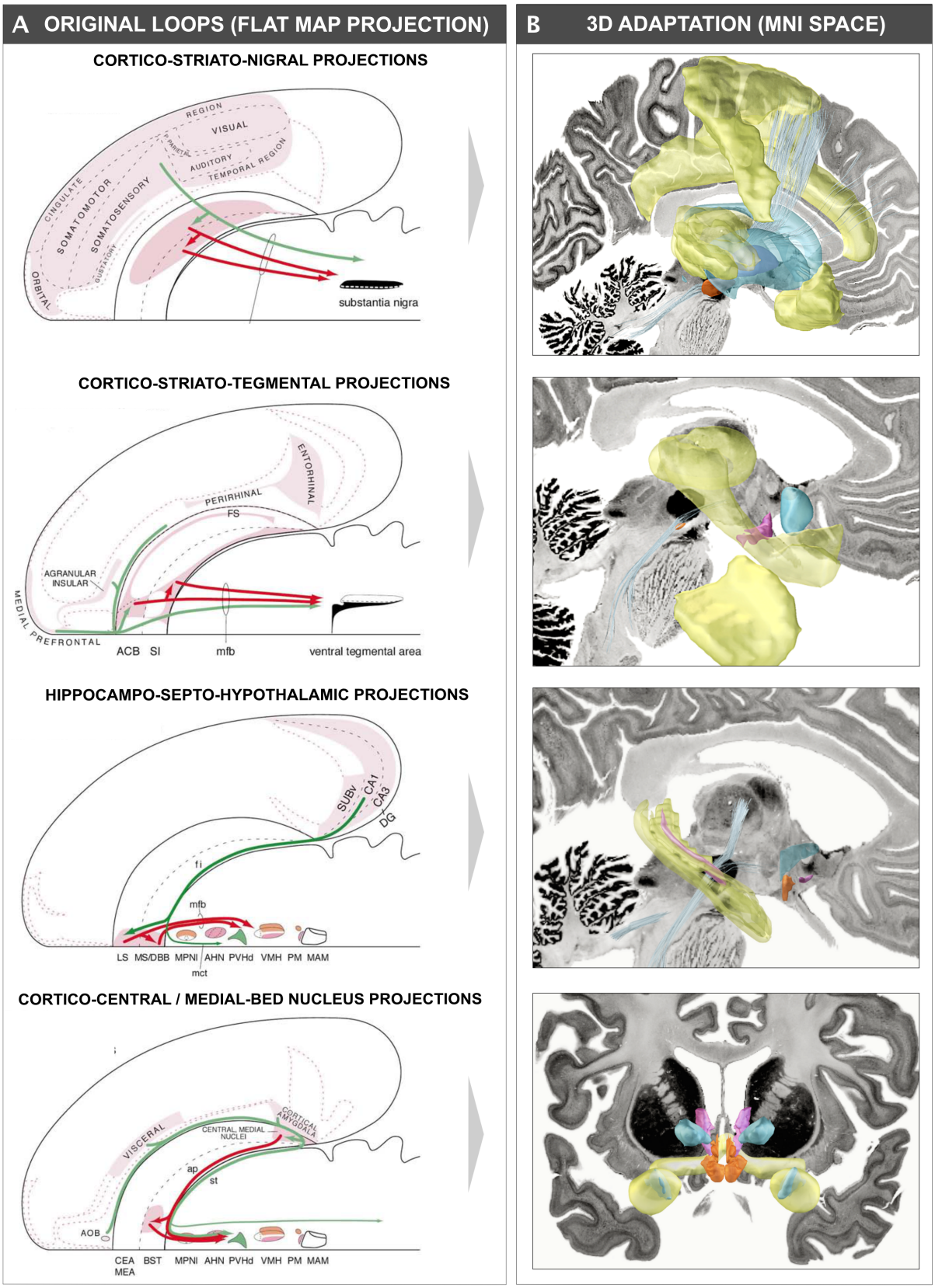


Fig. 2: Swanson's extension of the striatal and pallidal function to all cortical regions and brain nuclei. **(A)** Four loops as defined by Swanson (2003) are depicted. Each loop comprises tripartite projections with cortical (excitatory), striatal (inhibitory) and pallidal (disinhibitory) roles to regions within a behavioral

control column of motivated behavior. For instance, in the third loop shown, the lateral septal complex takes a “striatal” role, while the medial septal nucleus und nucleus of the diagonal band take the “pallidal” role. Note that the first loop would comprise both motor and associative loops depicted in **Fig. 1** – suggesting that Swanson’s loops should be further segregated. **(B)** We reproduced each Swanson loop on flat-map projections in 3D, with the BigBrain template shown as a backdrop (Amunts et al., 2013). Across all four loops, yellow regions indicate cortical, blue striatal, purple pallidal, and orange hypothalamic regions, while fiber connections are displayed in grey. Flat map projections in panel A reproduced, with permission, from original work (Swanson, 2000). *Abbreviations:* ACB, nucleus accumbens; AHN, anterior hypothalamic nucleus; AOB, accessory olfactory bulb; ap, ansa peduncularis; BST, bed nuclei stria terminalis; CA1/3, fields of Ammon’s horn; CEA, central amygdalar nucleus; fi, fimbria; FS, striatal fundus; LS, lateral septal complex; MAM, mamillary body; mct, medial corticohypothalamic tract; MEA, medial amygdalar nucleus; mfb, medial forebrain bundle system; MNI, Montreal Neurological Institute; MPN1, medial preoptic nucleus, lateral part; MS/DBB, medial septal/diagonal band nuclei; PM, premamillary nuclei; PVHd, descending paraventricular nucleus; SI, substantia innominata; st, stria terminalis; SUBv, ventral subiculum; VMH, ventromedial hypothalamic nucleus.

2.2. “Top-down” definition of therapeutic symptom network targets

While the bottom-up approach may provide a basis to tailor surgical interventions toward specific symptom domains, these concepts have not yet informed approaches in humans. In contrast, lesion studies and surgical interventions within deep brain targets have inspired some of the most influential cortico-basal ganglia models as well as the concept of circuitopathies and *symptom networks* (Bergman et al., 1990; Deffains et al., 2016; DeLong, 1990). Neuromodulation studies themselves may constitute a powerful way to probe and characterize changes along specific symptom dimensions across *symptom networks* (Fox et al., 2014; Horn and Fox, 2020; Siddiqi et al., 2021, 2020). DBS may be particularly suited, since i) stimulation sites are highly focal (i.e., specific), and ii) DBS exerts strong and long-lasting effects on symptoms. Specifically, by means of DBS, the acute and focal manipulation of a precisely targeted region that forms part of a network (*cause*) can be linked to a pronounced behavioral *effect* by their temporal sequence (Etkin, 2019, 2018).

In recent years, symptom network targets have been increasingly investigated on the group-level to harness DBS outcome variability: If electrodes in all top-responding patients fell into a particular network, but the same network was *not* targeted in poor-responding patients, researchers were able to infer a clear – and potentially causal – relationship between network modulation and overt effects (Horn, 2019; Horn and Fox, 2020).

As an example from the motor domain, the degree of structural connectivity between electrode sites and the supplementary motor area accounted for *bradykinesia* and *rigidity* improvements in PD patients receiving STN-DBS (Akram et al., 2017). On the contrary, it was possible to explain variance in *tremor* improvements based on the degree of stimulation applied to the cerebello-thalamo-cortical network. Studies in ET patients with DBS to the ventrointermediate thalamic nucleus associated the same network with tremor suppression (Akram et al., 2018; Al-Fatly et al., 2019). Extending this concept, Coenen et al. (2020) linked stimulation of the dentato-rubro-thalamic tract (DRT) with tremor improvements in ET, PD, multiple sclerosis, or dystonic tremor patients (**Fig. 3A**) – although disease-specific networks also appear to play a role (Tsuboi et al., 2021). Further subdividing this network based on somatotopy, optimal DBS for maximal treatment success in *head* versus *hand tremor* was related to modulation of *head* versus *hand* networks in primary motor area and cerebellum (Al-Fatly et al., 2019).

Similarly, studies have begun to map specific networks to DBS effects in the *neuropsychiatric* domain. In a prospective OCD trial, DBS to the anteromedial STN preferentially improved *cognitive flexibility*, mediated via connectivity to lateral orbitofrontal (OFC), dorsal anterior cingulate, and dorsolateral prefrontal cortices (Tyagi et al., 2019). In contrast, effectiveness of DBS to the anterior limb of the internal capsule (ALIC) in the same six patients was greater in ameliorating *mood* symptoms, underpinned by electrode connectivity to the medial OFC. A similar finding had previously been detected in MDD-DBS (Riva-Posse et al., 2014). A pathophysiological intersection in form of a reward network involving the medial OFC in both OCD (Figee et al., 2011) and MDD (Cheng et al., 2016) may

explain why patients affected by either disorder often benefit from DBS to the ALIC (which entertains connections to this circuit) (Figee and Mayberg, 2021).

In the study by Tyagi et al. (2019) – above and beyond their symptom-specific roles – both STN and ALIC targets were *similarly effective* in reducing global obsessive-compulsive behaviors in OCD patients. This implies a range of "optimal" entry nodes for pinpointing a shared therapeutic symptom network. Indeed, recent work by our group confirmed that stimulating both anteromedial STN and ALIC sites modulates a common network associated with effective DBS response. Specifically, this circuitry was characterized in form of a tract-based target in Li et al. (2020) and a volume-based functional network target in Li et al. (2021). The tract-based target has since been validated by other research groups (Baldermann et al., 2021; Smith et al., 2021; van der Vlis et al., 2021).

In accordance with the RDoC framework and as exemplified above for tremor or reward processing, some network targets may further span *across disorders* given phenotypical overlap along a *shared* symptom dimension. Published examples supporting such a transdiagnostic rationale in the neuromodulation context are given in **Fig. 3.** In the future, concepts like these could become increasingly useful to augment disease-specific strategies and encourage knowledge transfer between disorders (Cuthbert, 2014).

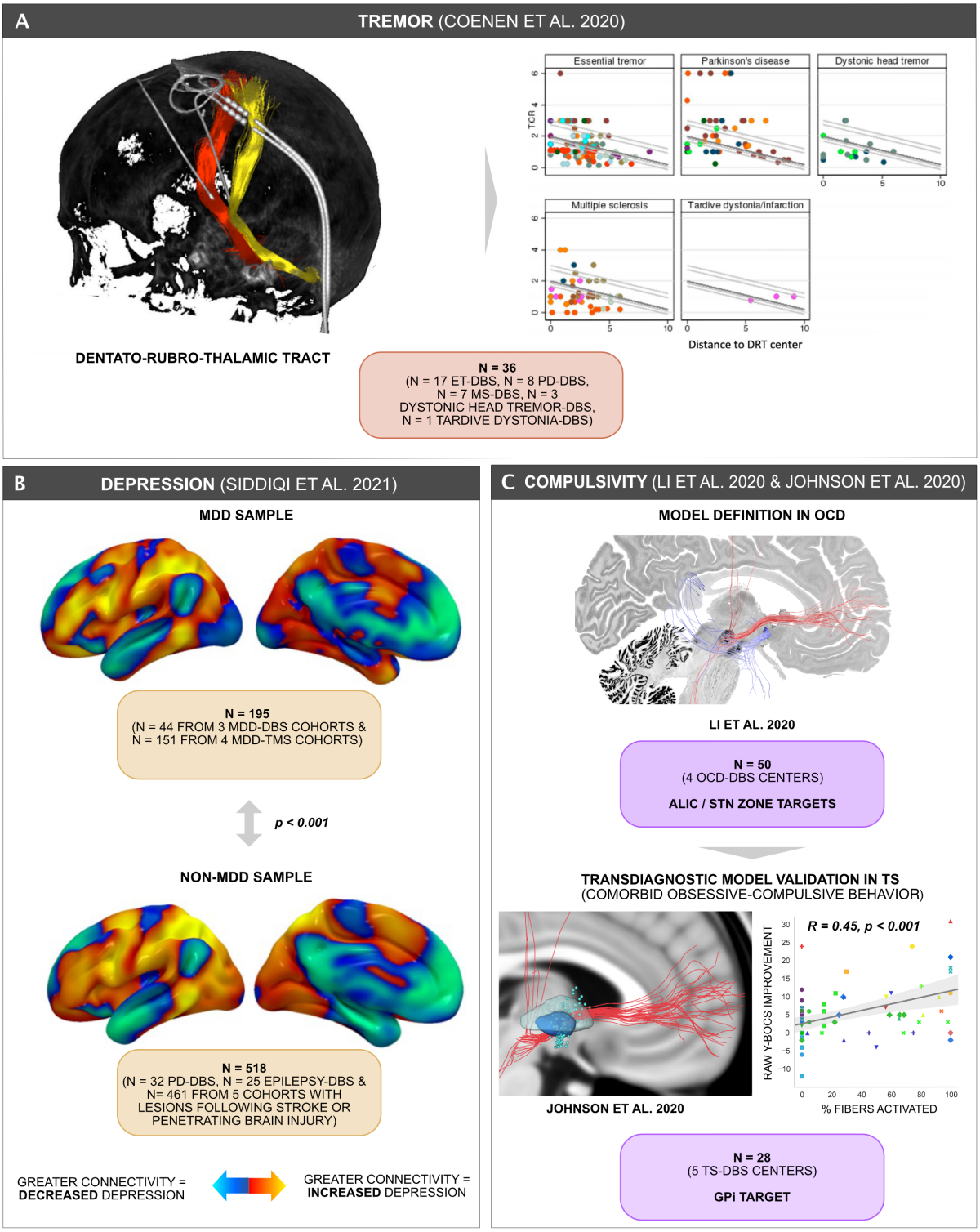


Fig. 3: Empirical examples of transdiagnostic symptom network targets. **(A)** In an observational case series, Coenen et al. (2020) probed the dentato-rubro-thalamic tract (DRT) as a common deep brain stimulation (DBS) target for tremor of differential origin (essential tremor [ET], Parkinson's disease [PD], multiple sclerosis [MS], dystonic head tremor, tardive dystonia). The current amplitude required for achieving tremor reduction (tremor improvement per current ratio [TiCR]) of patients who underwent tractography-assisted DBS was significantly ($p < 0.01$) negatively associated with the distance to both

DRT center (panel A) and border (not displayed here). **(B)** Siddiqi et al. (2021) demonstrated brain circuits associated with severity of depressive symptoms to be highly similar ($p < 0.001$) between i) a major depressive disorder (MDD) and ii) a non-MDD cohort, treated via different brain stimulation modalities or experiencing depressive symptoms following lesions of different cause. Specifically, a nearly identical network emerged when integrating a normative high-resolution connectome ($n = 1.000$) with connectivity seeds from i) antidepressant stimulation sites in patients treated for MDD via either DBS or transcranial magnetic stimulation (TMS), or from ii) either depression-inducing or antidepressant stimulation sites of patients treated with DBS for epilepsy or PD, and from depression-inducing lesions caused by penetrating brain injury or stroke. **(C)** Based on the degree of activation of a white-matter pathway that had initially been characterized as a unifying tract target in DBS for obsessive-compulsive disorder (OCD) for treating global obsessive-compulsive symptomatology (Li et al., 2020), Johnson et al. (2020b) were able to predict improvements of obsessive-compulsive behavior in Tourette syndrome (TS) patients with DBS to the globus pallidus internus (GPi). Importantly, the original tract target had been calculated on data of patients receiving DBS to either anterior limb of the internal capsule (ALIC) or subthalamic nucleus (STN) target zones, but not on GPi-DBS data. Figures in panel A adapted from Coenen et al. (2020) under a Creative Commons Attribution 4.0 International license (http://creativecommons.org/licenses/by/4.0/). Figures in panels B and C reproduced, with permission, from Siddiqi et al. (2021) and Baldermann et al. (2021), respectively. *Abbreviations:* Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

2.3. Defining symptom networks based on side-effects

While symptom network targets can be defined based on intended neuromodulation effects, the same can be achieved for undesired side-effects (Horn and Fox, 2020). In this context, Al-Fatly et al. (2019) associated networks with stimulation-induced ataxia and dysarthria using data of a cohort of 33 ET patients. In some cases, side-effects – such as hypomania in STN-DBS for PD (Coenen et al., 2009) – have even inspired novel treatment targets for different diseases such as MDD (Schlaepfer et al., 2013) and OCD (Coenen et al., 2017). Hence, modulating the same symptom network could lead to either desired or unwanted effects in dependence of the respective patient's pre-operative symptomatology.

Finally, some findings could potentially inform *"veto"* network targets (i.e., networks associated with DBS side-effects). On a focal level, reversal of detrimental DBS outcome could be achieved by decreasing the amount of stimulation to territory associated with stimulation-related side-effects (Frankemolle et al., 2010). Extending this focal concept toward circuit-level DBS, specific side-effect networks may be identified that should be avoided by DBS – for instance, such that have been associated with depressive symptoms in PD by Irmen et al. (2020), or with weight changes in patients receiving ALIC-DBS for treatment of OCD/addiction (Baldermann et al., 2019a). Similarly, networks associated with other symptoms, such as slurred speech, impulsivity (Mosley et al., 2020), panic (Elias et al., 2020), apathy (Boon et al., 2021), aggression (Yan et al., 2020), dysesthesia, or pain (Cury et al., 2020) should be spared by DBS.

2.4. Aggregating a library of symptom network target templates

The examples above illustrate the powerful use of DBS to subdivide network targets into distinct symptom domains, which could – once defined on the group-level – be tailored to a patient's individual phenotypical profile. Hence, we propose to identify symptom network targets by relating networks or fiber bundles activated by DBS to a symptom or side-effect dimension in question. For this purpose, we currently dispose of different resources (**info box A, Fig. 4**) and methods (**info box B, Fig. 5**). Ultimately, not only DBS but also other neuromodulation strategies or brain lesions could inform behaviorally selective networks, especially for concepts and behavioral traits inaccessible via DBS (e.g., spirituality (Ferguson et al., 2021) or criminal behavior (Darby et al., 2018)). An integration of multiple sources could additionally strengthen their reliability (Fox et al., 2014; Siddiqi et al., 2021).

By aggregating and continuously refining these templates we envision to establish a *library of symptom network templates* that could serve as a collection of building blocks for personalization. In view of the intention of *personalizing* DBS, establishing a *normative* symptom network target library, as a first step, may appear counter-intuitive. While this first

step can be conceived as a means of anchoring networks to function on a group-level, it is the consecutive two steps that aim at individualizing therapy.

Info box A: Connectomic resources

Owing to neuroimaging advances, we have become poised to scrutinize *in vivo* models of remote functional networks or white matter pathways activated by electrical stimulation. One frequently used method is diffusion-weighted magnetic resonance imaging (dMRI), which estimates white matter pathways based on the directionality of anisotropic water molecule diffusion along axons (Jeurissen et al., 2019; Maier-Hein et al., 2017). In contrast, resting-state functional magnetic resonance imaging (rs-fMRI) investigates spontaneous blood oxygenation level dependent (BOLD) signal fluctuations in individuals at rest as a function of the hemodynamic response in activated neuron populations (Fox and Raichle, 2007). The intention here is to identify conjointly (de)activating brain areas.

Both techniques can be used to estimate connectivity information either directly from a patient (*individualized* connectivity) (Akram et al., 2017; Baldermann et al., 2019b; Riva-Posse et al., 2018; Tyagi et al., 2019; Vanegas-Arroyave et al., 2016) or indirectly via *normative* connectomes acquired from an independent group of participants (Al-Fatly et al., 2019; Baldermann et al., 2019b; Calabrese et al., 2015; Cash et al., 2019; Horn et al., 2017; Irmen et al., 2020; Li et al., 2020; Riva-Posse et al., 2014; Weigand et al., 2018). Normative connectomes represent wiring atlases of the average healthy (or disease-specific) human brain that allow for robust global-scale insights (Wang et al., 2021), but lack information about individual anatomical/functional variance (Braga and Buckner, 2017; Finn et al., 2015; Gordon et al., 2017b; Kong et al., 2019; Llera et al., 2019). Prospectively, we see utility in both normative and individualized resources, the former to establish symptom network libraries, the latter to fine-tune them in individuals (**Fig. 4**).

Given that both dMRI and rs-fMRI are inherently limited by factors such as low test-retest reliability and susceptibility to false-positive tracts/voxels (Jeurissen et al., 2019; Maier-Hein et al., 2017), efforts have been directed towards alternatives to provide additional

anatomical detail. Histological templates (Alho et al., 2020), nonhuman tracer data (Haynes and Haber, 2013; Rohlfing et al., 2012), normative atlases curated by expert anatomists (Petersen et al., 2019), or text-book anatomy could be used in conjunction with existing strategies (Li et al., 2020; Treu et al., 2020). The major challenge in their application, however, is an accurate translation into patient space.

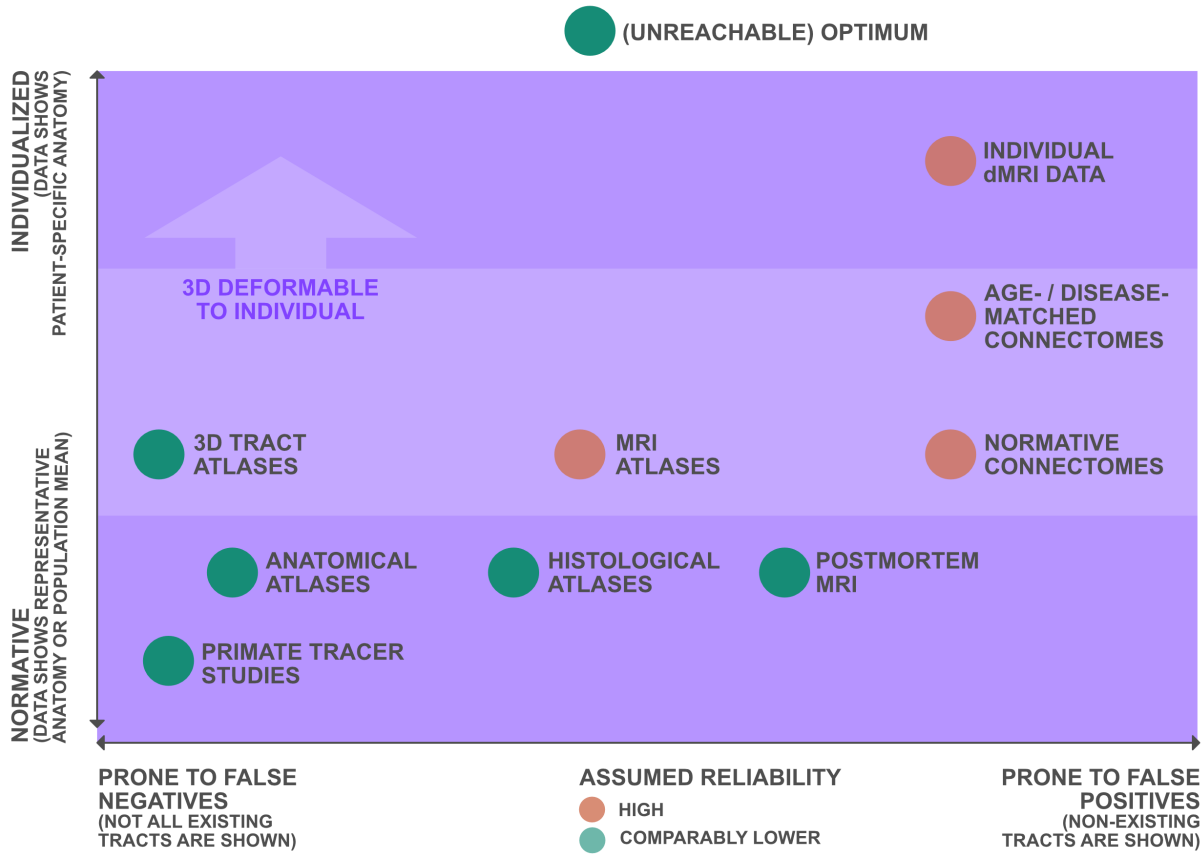


Fig. 4: Characteristics of tract-based connectomic resources for deep brain stimulation (DBS) network modeling. Available resources based on structural anatomy are compared as a function of their assumed reliability, their proneness to misrepresenting (i.e., over- or underrepresenting) empirically existing tracts, and how well they match individual anatomy. Resources that are defined in normative space could, in theory, be related to patient-specific anatomy (see bright box with arrow). Importantly, trade-offs are inherent to all these resources and one single, purely advantageous optimum resource is likely unachievable. Also note that this graph does not represent empirical data but is intended as a comparative and non-exhaustive graphical overview. *Abbreviations:* MRI, magnetic resonance imaging; dMRI, diffusion-weighted magnetic resonance imaging.

Info box B: Methodological primer to define network targets using DBS

To establish symptom network targets, connectomic DBS models can be linked to changes (i.e., pre- to postoperative/ON- versus OFF-DBS) in specific symptoms (Al-Fatly et al., 2019; Choi et al., 2015; Coenen et al., 2011; Horn et al., 2019, 2017; Okromelidze et al., 2020), behaviors (De Almeida Marcelino et al., 2019; Lofredi et al., 2021; Neumann et al., 2018), or side-effects (Baldermann et al., 2019a; Cury et al., 2020; Irmen et al., 2020; Mosley et al., 2020). Contributing prospective studies could be based on patient stratification into neurobiologically meaningful subtypes (Bell, 2014; Kapur et al., 2012) or dimensional symptom phenotyping. To ensure sufficiently powered retrospective investigations, the use of large repositories of pooled DBS data is advisable (Deeb et al., 2016; Synofzik et al., 2012).

We have proposed two methodological concepts to calculate DBS-based symptom network target templates which could be stored in a library for future use: i) *DBS fiber filtering* (Baldermann et al., 2019b) and ii) *DBS network mapping* (Horn et al., 2017). Code and graphical user interfaces for both these methodological strategies are openly available within Lead-DBS software (www.lead-dbs.org).

DBS fiber filtering (**Fig. 5B**) aims at answering the question which *structural fiber tracts* account for changes in a certain symptom during electrical stimulation. The resulting tract represents the optimal connectivity profile of DBS electrodes for maximized symptom improvement – or "veto" tracts associated with undesirable side-effects. This *tract-based* method has, for instance, been employed to cross-predict variance in OCD-DBS (Baldermann et al., 2019b; Li et al., 2020), or depressive DBS side-effects in PD (Irmen et al., 2020).

While *DBS fiber filtering* allows to visualize one segregated network link (or *edge*) associated with clinical DBS effects, the method is agnostic to potential *indirect* connections to brain regions (or *nodes*) within widely distributed whole-brain networks. DBS network mapping (**Fig. 5C**) can overcome this limitation by incorporating rs-fMRI data representing BOLD signal changes across wide-spread brain regions. This *voxel-based* approach has been used to create DBS symptom network models in PD (Horn et al., 2019b, 2017; Irmen et al.,

2020), ET (Al-Fatly et al., 2019), OCD (Baldermann et al., 2019b; Li et al., 2021; Sheth et al., 2013), epilepsy (Middlebrooks et al., 2018), or dystonia (Okromelidze et al., 2020).

Of note, some targets (such as the STN) may be more suitable for investigation by specific modalities (such as tractography) compared to others (such as the GPi). In this specific example, a limitation of tractography for GPi targeting resides in close proximity of the internal capsule which would lead to false-positive fibers not connected to the GPi (Beukema et al., 2015). Instead, the STN is known to receive direct cortical input exactly via axon collaterals traversing the internal capsule (Nambu et al., 2000, 1997, 1996). Hence, not all concepts developed for one target (such as the STN) may be directly applicable to other target regions (such as the GPi). Other modalities (such as functional connectivity) could be better suited for application across the two targets, as recently demonstrated (Sobesky et al., 2021).

The resulting streamlines or R-maps could be stored in form of three-dimensional objects within a *symptom network target library* (**Fig. 5D**), precisely defined in a standard brain template atlas. Important steps toward replicable, neurocircuit-based stimulation correlates could consist of making initial network target atlases available for validation/falsification by other researchers. Several studies have already successfully adopted this workflow (Johnson et al., 2020; Mosley et al., 2021; Smith et al., 2021).

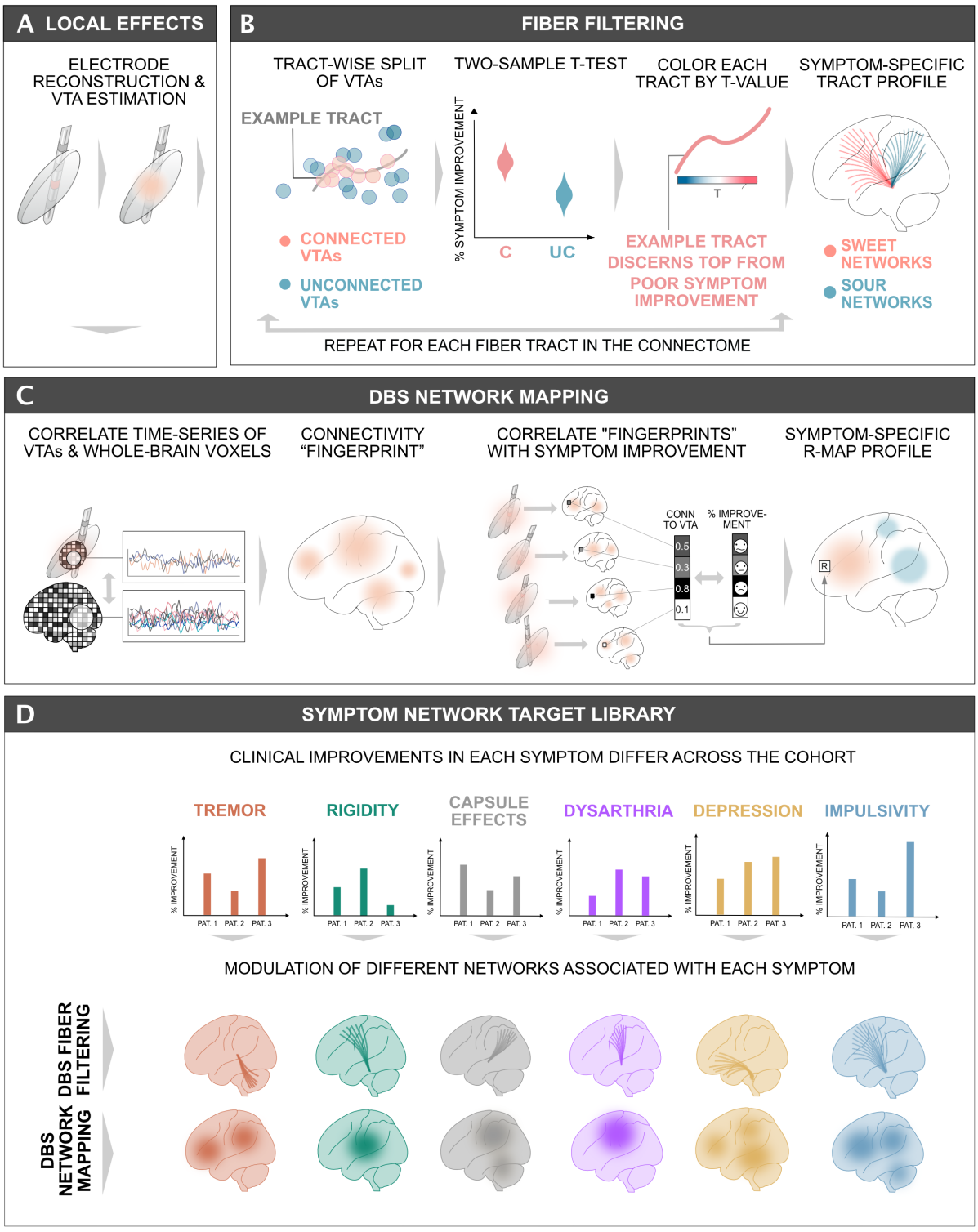


Fig. 5: Modeling strategies for deep brain stimulation (DBS) symptom network target templates. **(A)** A network model of DBS effects onto specific clinical outcome parameters can either be estimated on a tract- or voxel-level. In both cases, electrodes are first reconstructed in stereotactic standard space and volumes of tissue activated (VTAs) by the electrical current are estimated. **(B)** In the tract-based approach (Baldermann et al., 2019b), patients are first grouped as a function of whether their VTAs are *connected* (C) or *unconnected* (UC) to a specific fiber tract. Then, the *t*-value resulting from a statistical

comparison between symptom improvement values of both groups is used to color-code the respective tract (here, *red* illustrates tracts associated with stimulation-dependent symptom improvement, while *blue* indicates worsening). This procedure is repeated across the connectome, leading to a symptom-specific model of "optimal" structural electrode connectivity for maximal clinical improvements. *Sweet networks* represent coordinates alongside fiber tracts associated with favorable stimulation outcome, whereas *sour networks* are linked to detrimental DBS effects. **(C)** In the voxel-based approach (Irmen et al., 2020), correlations of mean time-series of voxels within each patient's bilateral VTAs with every remaining whole-brain voxel are performed on a voxel-by-voxel basis. In view of individual differences in localization of active electrode contacts (owing to variability in precise electrode placement and stimulation parameter programming), this procedure results in one unique functional connectivity (FC) *"fingerprint"* per patient. Voxel-wise correlation of these patient-specific fingerprints with symptom improvements across the patient sample leads to an "optimal" *R-map* model associated with maximal symptom improvement (here, *red* codes for brain regions to which DBS electrodes should ideally connect, while *blue* indicates such areas to which DBS electrodes should optimally be anticorrelated, to ascertain best possible outcome). **(D)** The resulting structural or functional, symptom-specific connectivity models may finally be integrated into a comprehensive, neurocircuit-based taxonomy of DBS effects, which – after thorough replication and refinement – may serve as a neurobiologically meaningful basis for personalization. *Abbreviations:* Conn, connectivity; Pat., patient.

3. Template matching: re-discovering symptom networks in individual patients

After defining a template library of symptom network targets, the latter could be re-discovered *within an individual brain* by matching each group-level library entry to intrinsic networks in the respective patient's brain (**Fig. 6**). We refer to this process as *"template matching"*. Specific approaches of realizing exactly this concept (referenced by the same term) have been developed for applications outside of the neuromodulation field (Gordon et al., 2017b, 2017a).

In the DBS context, exploration of the concept and methodological workflows for matching network templates to patient-specific brain anatomy is only beginning to gain traction. One of the few prominent examples is template matching of individualized tracts in MDD-DBS patients to a reference (or "*blueprint*") set of connections that have been termed the *"depression switch"* (Choi et al., 2015). In this line of studies pioneered by the Mayberg group, modulating a set of white matter tracts (forceps minor, cingulum, uncinate fasciculus [UF], and fronto-striatal fibers) was associated with optimal improvement of depressive symptoms following DBS of the subcallosal cingulate cortex (SCC) (Riva-Posse et al., 2014). This set of tracts was defined as a *template* but re-identified using dMRI-based tractography in *individual* patients and prospectively targeted (Riva-Posse et al., 2018).

Similarly, Coenen and colleagues used individualized tractography in MDD patients to identify the ventral tegmental area-projection pathway as a specific tract target (Coenen et al., 2018, 2017; Schlaepfer et al., 2014, 2013), which had been serendipitously defined in a PD patient with hypomania (Coenen et al., 2009). Further, they pioneered prospective targeting (and intraoperative use of diffusion tractography) in ET by stimulating the DRT as defined in individual patients (Coenen et al., 2011). **Info box C** contains a primer on methodological avenues toward template matching.

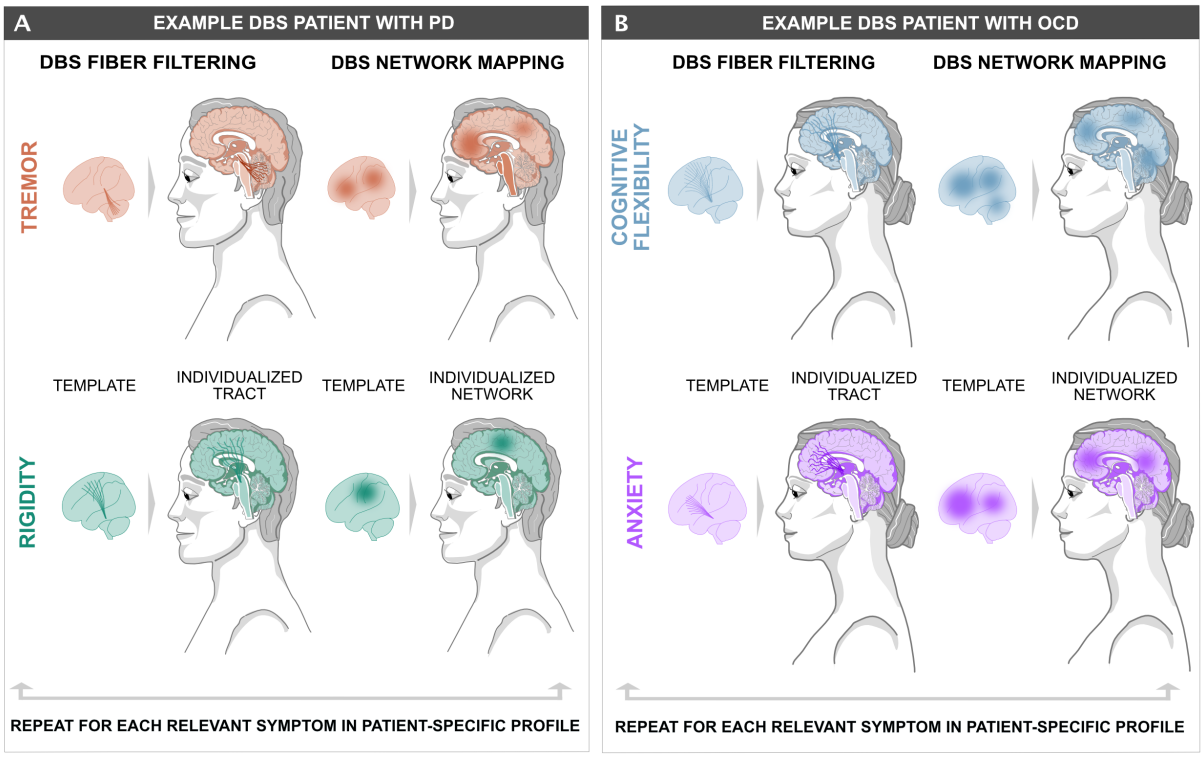


Fig. 6: Template matching for application in deep brain stimulation (DBS). Group-average symptom network target templates for DBS with relevance to a patient's unique symptom profile could be queried from the normative library and matched to networks defined in an individual patient. Two example patients are shown, of which one is affected by Parkinson's disease (PD; **panel A**) and the other by obsessive-compulsive disorder (OCD; **panel B**). Depending on the method used to derive the respectively selected templates, multiple strategies are conceivable for template matching, including – *inter alia* – inverse normalization or independent component analysis. While several approaches to template matching have already been probed in other research fields, the precise details of these methods remain to be established and validated in the DBS context.

Info box C: Methodological primer to match individual networks to symptom templates

Once a library of symptom-specific tracts is established, one could re-discover the respective tracts in individuals as proposed by the Petersen, Mayberg and Coenen groups. Manual identification of tracts in individual brains or landmark seedings based on template tract definitions could facilitate this process. In contrast, fully data-driven approaches could involve whole-brain tractography in individuals (Reisert et al., 2011) and subsequent tract-wise rating based on spatial similarity of the (coregistered) template tract (e.g., via root mean square distances/k-nearest-neighbor searches across tract-defining points). In this context, automatic tractography and shape-analysis may be useful to re-identify tracts in individuals (Yeh, 2020).

In the functional domain, two candidate approaches can be differentiated: i) scanning functional networks at rest (rs-fMRI) and ii) deriving BOLD signal fluctuations during task performance. In the former, we would aim to find the intrinsic brain network (based on individual rs-fMRI acquired in an individual patient) which best matches the template. Concepts such as independent or principal component analysis have helped clustering intrinsic brain activity into subnetworks (Calhoun et al., 2008; Smith et al., 2012). These subnetworks could be compared to target network templates using distance metrics. Similar approaches for template-matching have applied seed-based connectivity concepts (Gordon et al., 2017a, 2017b). On the other hand, tasks related to the symptom of interest could be investigated via task-based fMRI. For instance, Barcia et al. (2019) used a patient-specific symptom-provocation paradigm to identify treatment networks in OCD. Similarly, Anderson et al. (2011) elucidated patient-specific regions of interest in the motor cortex and superior cerebellum via a finger-tapping task to derive individualized thalamic DBS targets for treatment of ET.

4. Network Blending: Toward personalized connectomic DBS

After their re-identification in the individual patient, symptom networks represent valuable resources to adapt DBS targeting and stimulation parameter programming strategies to a patient's unique symptom profile (Horn and Fox, 2020). For a future of individualized DBS, we envision preoperative phenotyping alongside various dimensional symptom axes to inform i) the prevalent *symptom profile* of a specific patient, and ii) the selection of a set of corresponding DBS symptom network targets along with undesirable networks to be avoided by the stimulation (associated with either "classical" DBS side-effects or unwanted symptoms) (**Fig. 7**). The preselected network targets could then iii) be weighted to account for relevant factors beyond empirical symptom intensities, and, finally, iv) be synthesized into a DBS network target tailored to the needs of the individual patient. We term this final and essential personalization step "*network blending"*.

Naturally, spatial relationships between symptom networks will influence the ease of optimally stimulating the selected set of network targets at a time. In cases where relevant symptom networks are intersecting, networks could be *blended* to identify stimulation sweet spots. While methods are likely to become more elaborate over time, we propose a simple linear weighting of symptom networks (**Fig. 7**). An optimal electrode implantation coordinate or stimulation parameter setting would maximize stimulation of *relevant* symptom network targets with highest weights while avoiding stimulation of side-effect networks. In complex cases with non-adjacent symptom networks, current steering via directional electrodes or secondary targets could be suggested. The latter may involve non-conventional trajectories, multiple electrodes or electrodes that reach different regions in one pass. **Info box D** introduces these potential network blending strategies.

To name an example of how personalized targeting has been achieved via network blending, the circuit-based "depression switch" target was recently successfully refined by use of directional electrodes in a patient with posttraumatic stress disorder (PTSD) (Hamani et al., 2020). While the confluence of the cingulum bundle, forceps minor, fronto-striatal tracts and UF in the SCC had originally been successfully exploited for treatment of MDD with primary

depressive symptoms (Riva-Posse et al., 2018, 2014), the UF appears to play a crucial role in primary anxiety (Baur et al., 2011; Harnett et al., 2020; Phan et al., 2009). Additional hints toward the UF-hypothesis could further be derived from a previous case report on a patient with PTSD where DBS to the basolateral amygdala – which connects to the ventral prefrontal cortex via the UF (Thiebaut de Schotten et al., 2012) – proved effective in relieving anxiety symptoms (Langevin et al., 2016). Hence, the surgical team around Hamani et al. (2020) placed electrodes in a way that one contact centered around the "depression switch" blueprint (medial SCC) and another contact near the UF (lateral SCC), allowing for concurrent improvement of depression and anxiety symptoms. Evidently, future studies including larger samples are needed to confirm safety and generalizability of this effect for treatment of co-existing symptoms in PTSD.

Further, we propose a personalized weighting step such that a set of cardinal symptoms could form the *treatment focus*, while additional comorbidities could be treated with lesser importance (i.e., weights could be applied based on empirical intensities of preoperatively experienced symptoms). For example, preponderant tremor in one PD patient could shift the treatment focus toward maximized stimulation of the tremor network. By contrast, modulation of bradykinesia and rigidity networks may weigh more heavily in another PD patient. Moreover, importance of side-effect networks may vary across individuals. While cognitive impairment or affective symptom networks should be avoided in all patients, their avoidance could receive even stronger emphasis in late-stage PD patients that already experience these symptoms. Similarly, beneficial networks could not only be weighted based on symptom severity, but also based on individual preferences. For instance, some patients may experience tremor as a stronger subjective burden than bradykinesia, or vice versa.

Since most symptom libraries will be defined based on conventional DBS target sites (e.g., the STN), the primary symptom of a patient could dictate the broader implantation zone in focus. For example, for an MDD patient of sadness-dominant type (*high negative affect*) SCC stimulation might represent an optimal strategy for recalibrating ventromedial prefrontal cortex projections (Figee and Mayberg, 2021). By contrast, an MDD patient experiencing

predominant anhedonia (*low positive affect*) could benefit more from stimulation to circuitry involving the nucleus accumbens-ventral internal capsule area (Scangos et al., 2021).

Variability in volume and topographical distribution of functional sub-territories within these conventional target structures, along with their anatomical position relative to adjacent nuclei and pathways, will supposedly play an essential role in the ease of implementing network blending. For example, the human STN (with a volume of approximately 240 mm^3) is of considerably smaller size as compared to the GPi (with a volume of approximately 957 mm^3) (Hardman et al., 2002). Consequently, coverage of a more comprehensive set of relevant PD symptom networks by use of a single VTA could be possible within this target structure. This fact, however, coincides with an increased likelihood of hitting associative or limbic side-effect networks during optimization of the therapeutic effect.

On a more granular level, we expect coordinate peaks *within* these target structures in dependence of the respective symptom profile. As a concrete example, we anticipate an optimal coordinate for tremor suppression at more dorsal and posterior levels (slightly outside the STN), whereas a maximal bradykinetic effect could reside more ventrally, within STN proper (Boutet et al., 2021; Roediger et al., 2021). Of note, precautions are due when interpreting evidence on stimulation sweet-spots, as it remains limited by tissue contrast, spatial resolution, and the signal-to-noise ratio of currently available (clinical) imaging protocols (Horn, 2019). This is especially relevant for DBS targeting where slight misplacement of electrodes (i.e., by a mere 2 mm) can already entail poor therapeutic outcome (Bot et al., 2018; Horn et al., 2019a).

Finally, the proposed personalization framework could facilitate harmonization with different forms of neuromodulation, such as other invasive methods (e.g., gamma-knife surgery) or non-invasive forms of brain stimulation, pharmacotherapy, or behavioral interventions (e.g., cognitive-behavioral therapy or neurofeedback) (**Fig. 8**). For instance, invasive and non-invasive brain stimulation modalities could be used to steer shared therapeutic network effects from different vantage points (Fox et al., 2014; Siddiqi et al., 2021) or to access symptom-specific circuits (Crocker et al., 2013; Shephard et al., 2021). Hence,

multi-modal strategies such as brain stimulation combined with pharmacotherapy (Sharma et al., 2012), psychological/behavioral interventions (Görmezoğlu et al., 2020; Mantione et al., 2014; Tyagi et al., 2019), light therapy (Weigand et al., 2021), or physical exercise (Miterko et al., 2021) could be of use for optimally tailoring interventions to symptom heterogeneity by balancing modality-specific effectiveness.

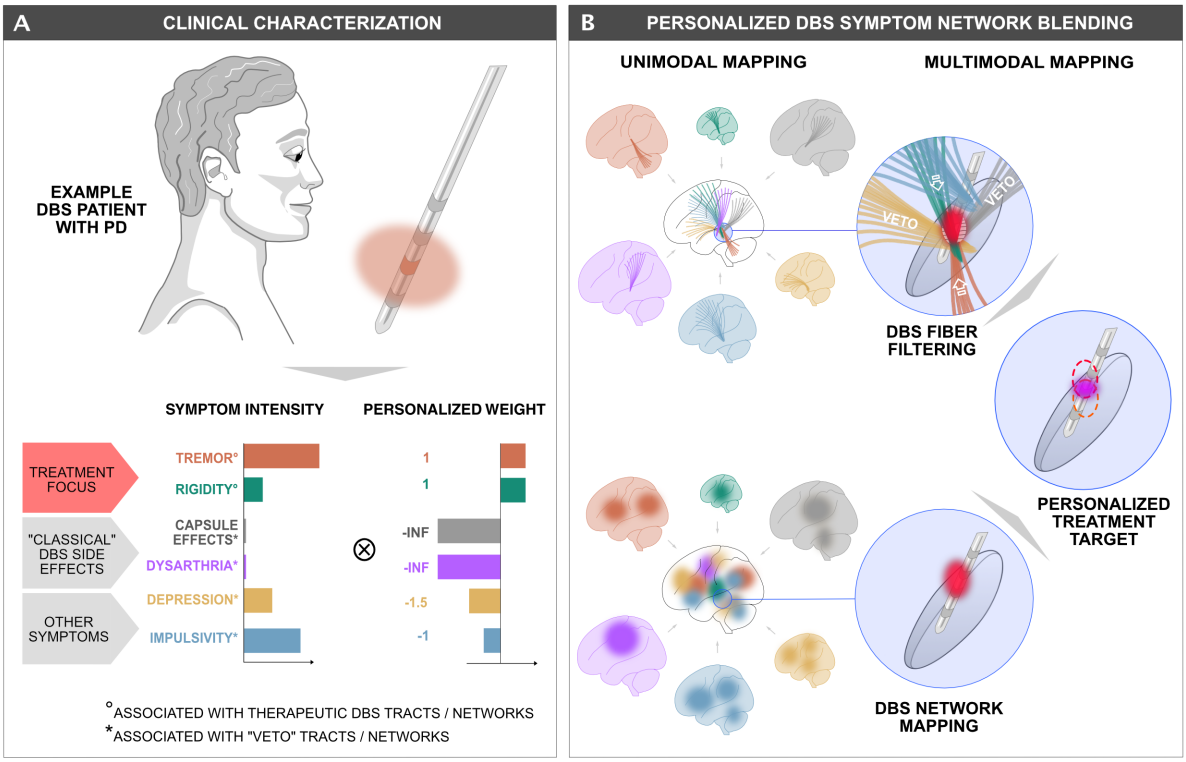


Fig. 7: Personalized deep brain stimulation (DBS) symptom network blending. (**A**) In a first step, the prevalent symptom profile of a patient is characterized along different dimensional axes as a function of their respectively experienced intensities. Based on the resulting clinical symptom profile, a corresponding set of therapeutic DBS circuit targets, as well as "veto" networks could be queried from the symptom network template library. Although several cardinal symptoms will form the treatment focus, "classical" DBS side effects can be considered as well as other symptoms that may be present in the patient prior to surgery. In addition, a personalized weighting step could allow to further fine-tune the patient's treatment profile. While side-effects would be attempted to be avoided as much as possible in all patients, a patient's personal circumstances, preferences and needs could also be incorporated at this stage. (**B**) In a second step, a personalized stimulation coordinate most beneficial for the unique phenotype of this patient could be achieved by weighting, synthesizing, and blending the selected

symptom network target templates and "vetoing" side-effect targets (which have ideally already been matched with individualized connectivity of the patient in question during the *template matching* step). This "weighting-and-blending" strategy could theoretically be applied to target templates derived via either DBS fiber filtering or via DBS network mapping. Thus, in a final step, optimal stimulation coordinates proposed for each of these modalities separately could be integrated into one most optimal, patient-specific stimulation target. *Abbreviations:* PD, Parkinson's disease.

Info box D: Methodological primer for DBS network blending

In view of increasing degrees of freedom in the parameter space, a (semi-)automated algorithm could represent the most efficient way of exploiting the therapeutic window to suggest optimal DBS stimulation sites. Symptom intensity weighting could be performed on either a voxel- or a tract-level (depending on the method underlying the selected network target templates). An optimal stimulation coordinate could be based on maximal overlap with fiber tracts/voxels with highest weights. Such an algorithm would optimally also account for other priors of DBS effectiveness to achieve most precise predictions. For instance, patient-specific factors (such as age, disease progression, or medication) may explain additional amounts of variance in clinical outcomes (Cavallieri et al., 2021; Guzick et al., 2020; Shalash et al., 2014).

Crucially, *expert decision making* will be needed to supervise and interpret results in any scenario, even more so if no clear peak stimulation target can be identified. Suggested stimulation sites residing largely outside established treatment targets would need to be disregarded or further investigated in basic research. In some cases, proposed anatomical sites may also be strategically inaccessible via DBS leads. Practically speaking, we see direct benefit of the approach to refine existing target sites (such as subzones within the STN/ALIC), rather than to suggest novel targets (which may still bear high interest for basic research).

Personalized network target models could be probed first on retrospective datasets through basic research, cross-validations on retrospective data, or in virtual simulations (Meier et al., 2021). Once established, and only after careful validation, these concepts could inform prospective controlled clinical trials investigating suitability of the proposed strategy to guide DBS programming and surgery – or its superiority as compared to conventional targeting

approaches. Given the reversible nature of DBS programming, the ethical implications would be lower, and this strategy could be applied before their use to refine surgical planning (which entails results that are not easily reversible). In DBS programming, new generations of directional electrode models could be leveraged to precisely steer the electrical field toward therapeutic and away from side-effect networks (Steigerwald et al., 2016). In view of possible dynamical changes in symptom constellations over time (e.g., following neurodegeneration), directional leads also allow for pre-implant planning with adjustments per time to anticipate future needs.

Ultimately, the proposed personalization concept could be translated into clinical care. In some cases, multi-focal strategies could help to modulate symptom-specific networks from different angles (Figee and Mayberg, 2021; Li et al., 2021, 2020; Scangos et al., 2021; Tyagi et al., 2019). The effectivity of a one-pass thalamic-subthalamic trajectory of DBS electrodes has, for instance, been investigated for concurrent treatment of tremor, rigidity and bradykinesia (Coenen et al., 2016; Neudorfer et al., 2019; Reinacher et al., 2018). Besides single-electrode strategies, co-stimulating distinct symptom networks could be achieved via multiple electrodes at non-adjacent sites, as during concomitant DBS to the GPi and STN (Sriram et al., 2014).

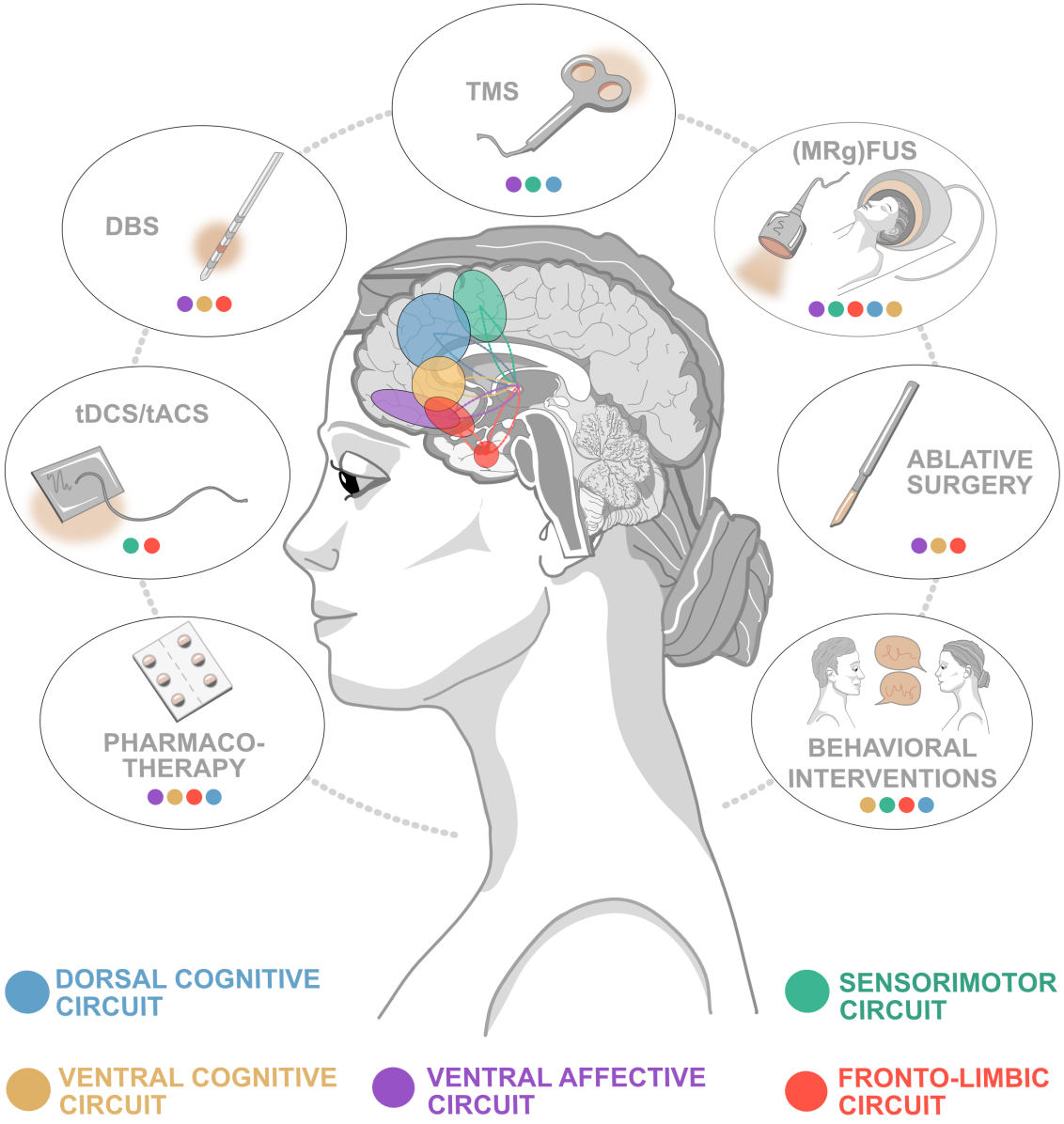


Fig. 8: Different treatment strategies (including neuromodulation modalities) may show differential effectiveness to impact specific symptom networks. This concept is visualized here on the example of obsessive-compulsive disorder (OCD) based on an extensive literature integration proposed by Shephard et al. (2021). In OCD, these networks may be affected to varying degrees in individual patients – as a result forming heterogeneous OCD phenotypes. Once properly defined on a group level and re-identified in the individual patient, these may serve as potential targets to tailor treatment to a patient's unique symptom constellation. Crucially, specific (multimodal) treatment strategies may be particularly suited to treat each of these symptom networks, extending the proposed personalization framework beyond invasive neuromodulation. *Abbreviations:* DBS, deep brain stimulation; MRgFUS, Magnetic Resonance-guided Focused Ultrasound; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

5. Limitations and future challenges

While further research is needed to carve out symptom-specific DBS network-effects, this blueprint constitutes an initial steppingstone toward circuit-based personalization of DBS. Many limitations apply which could, however, inspire future refinement of the suggested rationale and its underlying assumptions.

First, our approach assumes additive effects of DBS onto different symptom clusters and associated networks. By contrast, cortico-subcortical loops dynamically interact at different levels to generate the multifaceted psychological experiences and behaviors at the root of intricate phenotypes (Aoki et al., 2019; Guthrie et al., 2013; Kolomiets et al., 2001). On the other hand, interactional effects may also prove advantageous when aiming to simultaneously account for multiple symptoms. Moreover, conclusions cannot be drawn about white-matter target engagement via the here-proposed methods. In future studies, potential biomarkers could be identified as a means of confirming post-operative propagation of electrical stimulation through target networks (Waters et al., 2018).

Second, current models of tissue activation are unable to account for the complex amalgamation of local and remote physiological DBS effects, comprising oscillatory, neuroprotective or neurochemical effects, ionisation of molecules, intracellular mechanisms, influence on glia cells, as well as synaptic plasticity or network reorganization (Ashkan et al., 2017; Herrington et al., 2016; Lozano et al., 2019; McIntyre et al., 2004; McIntyre and Anderson, 2016; Veerakumar and Berton, 2015a). Similarly, all DBS-related studies discussed herein applied high-frequency (i.e., >100 Hertz) stimulation, which produces effects resembling those of focal lesions (Neumann, 2021). However, this first-order approximation neglects the impact of frequency, pulse width, excitatory/inhibitory effects, or differential entrainment of fiber types of variable myelination. Effects of lower and/or variable and adaptive stimulation frequencies may have largely differing – or even opposing – effects (Benabid et al., 1991; Fox et al., 2014; Krauss et al., 2021; Neudorfer et al., 2021). Further, different disorders – even those that respond to high-frequency DBS – may not necessarily present with a common

pathology. Accordingly, methodological refinements of tissue activation modeling and pathophysiological investigations could increase predictive precision.

Third, evaluations of DBS network effects via diffusion tractography-based fiber reconstructions remain limited in their anatomical accuracy and reliability (Le Bihan et al., 2006; Maier-Hein et al., 2017; Schilling et al., 2019; Thomas et al., 2014). This is due to theoretical assumptions and practical constraints (such as scanning considerations or processing/tracking algorithms) that are exacerbated in the case of small and neuroanatomically complex structures (Thomas et al., 2014). Consequently, confirmation studies of anatomical correspondence via external resources have produced mixed results for different subcortical pathways (Jakab et al., 2016; Sedrak et al., 2008; Sudhyadhom et al., 2013). Nevertheless, *in vivo* diffusion tractography-guided white matter targeting has been successfully used for optimizing accurate intraoperative targeting (Coenen et al., 2014, 2011; Schlaepfer et al., 2013), with particular benefit for white-matter targets which cannot be reliably identified via conventional MRI (Bhatia et al., 2012; Hunsche et al., 2013). Going forward, controlled clinical trials along with surgical planning software packages including probabilistic tractography are warranted to evaluate dMRI-guided DBS surgery against conventional targeting approaches (Oxenford et al., 2021).

Fourth, collaboratively defining a library of DBS network targets challenges standardization and pathophysiological relevance in the design of symptom assessment batteries. Because symptom constructs are subjective, prone to fluctuations, and objective metrics or diagnostic criteria often lacking, quantifiability and relatability to connectomic biomarkers may be complicated (Odgers et al., 2009; Prange et al., 2019; Sullivan et al., 2021; Vergunst et al., 2013). A reliable and sparse collection of dimensional assessments will rely on critical examination and regular updating to avoid infinitesimal symptom axes with decreasing clinical utility (Morris and Cuthbert, 2012).

Fifth, symptom patterns and intensities may change over natural disease trajectories (Cilia et al., 2020; van Eeden et al., 2019). Also, postsurgical onset of stimulation effects may be delayed in some disorders (Krauss et al., 2004; Lozano et al., 2019; Veerakumar and Berton,

2015b), and tachyphylaxis, habituation (Benabid et al., 1996), or disease-modifying effects could emerge (Cif et al., 2013). Since many diseases treated by DBS technology are chronic or of neurodegenerative nature, preoperatively irrelevant symptoms might emerge and set the stage for future suboptimal personalization (Figee and Mayberg, 2021). While these factors underline a necessity to consider ongoing adjustments, the latter could also undermine the stability of DBS effects, favoring a “set-it-and-forget-it” strategy.

Sixth, neither will it be possible nor intended to treat each preoperative symptom with equal importance. Practical factors such as target/device certificates, psychosocial and socioeconomical circumstances, ethical concerns and the treatment’s risk-benefit profile may critically weigh into interventional decisions (Accolla and Pollo, 2019; Kubu and Ford, 2017; Shephard et al., 2021). Also, neither will all patients or disease subtypes be eligible for DBS nor all symptoms accessible via this approach.

Last, precise DBS targeting is a critical first step to reduce outcome variance, which will promote the management of residual symptoms. Clearly, however, accounting for contributors to DBS outcome above and beyond electrode localization and associated connectivity will critically increase interventional precision.

6. Conclusions

The present whitepaper proposes a three-step framework for network-based personalization in neuromodulation based on i) establishing and ii) individualizing symptom-specific network targets. These can subsequently iii) be synthesized (or “*blended*”) into personalized treatment targets tailored to the symptom profiles of an individual patient. While methodology for step i) has been developed and validated in the past, translational research is currently invested in refining methodological details for steps ii) and iii). In conclusion, we believe that this concept provides a powerful avenue toward advanced neuromodulation for two major reasons: First, it allows to systematically model *precise* connectomic predictors of stimulation effects onto various symptom dimensions. Second, it promotes interventional *personalization* to symptom heterogeneity.

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Declaration of competing interests

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CRediT author statement

BH and AH: Conceptualization, Writing – Original draft preparation, Visualization, Funding acquisition; NR: Writing – Reviewing and Editing, Visualization; SHS, CF, KB, AAK, HM, MDF, CN: Writing – Reviewing and Editing.

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