Connectomic Deep Brain Stimulation for Obsessive-Compulsive Disorder

Supplement

Methodological approaches to model pathways of effective DBS

Stimulation through DBS electrodes modulates surrounding neural tissue as a function of the applied electric potential. The spatial extent of neural activation is often referred to as the *stimulation volume* or *volume of activated tissue* (VAT). Determining the exact spread of the electric current and establishing boundaries that indicate whether or not an axon is activated is far from trivial and each binary representation (i.e. sphere drawn around an electrode) is a drastic oversimplification of differential effects that may arise (e.g. in dependence of axonal orientation or diameter, degree of microscale anisotropy, neurotransmitters, glia cells etc.) (1). Still, different models to calculate individual VATs are now available that represent a best possible approximation and have shown to be useful in specific contexts (2). In order to identify an optimal stimulation target or *sweet spot*, one can map clinical effects directly onto VATs and aggregate data in a probabilistic fashion across patients (3,4). However, since several distant targets have been effective in OCD, the optimal target site might better be represented by a white matter tract – or a distributed whole-brain functional network. In such a case, two VATs that do not overlap (e.g. if they originate from two different surgical target regions) might still be part of the same pathway or network – which would not be captured by a conventional *sweet spot* analysis. Instead, – in analogous nomenclature – an *optimal tract* or *network* analysis would be necessary to explain these effects in the same model. Undeniably, classic analysis of *sweet spots* can further complement such network analyses to characterize or validate specific hubs within a given network. In the case of DBS for OCD, network analysis is of specific interest, given that different target regions have yielded comparable clinical improvements, suggesting a commonly modulated network.

A combination of electric field models and brain connectivity estimates can be used to carry out such analyses. dMRI is a widely used technique to study structural connectivity in humans in vivo. Based on directionality of anisotropic diffusion of water molecules in brain tissue, this approach renders streamlines that estimate the general direction of white matter tracts at any given voxel. Alternative concepts such as histological mesh tractography (5) or atlas datasets based on expert knowledge (6) have been proposed, and each method has their unique advantages (7). Different approaches to combine models of white matter anatomical distribution with models of OCD DBS have been proposed, with the final aim to study specific clinical effects on a group level (text box 1). Other approaches have been reported in DBS for movement disorders or depression (e.g. 35, 37) but are not discussed herein.

Functional connectivity based on resting-state fMRI constitutes a further approach to study connectomic DBS (e.g. (10,11).

OCD DBS studies have used both individual and normative connectomic dMRI approaches, each with benefits and limitations. The most intuitive strategy is to use individually acquired dMRI scans of the OCD patient undergoing surgery for the analysis of structural connectivity. However, acceptable dMRI scans may not always be available from each patient since high quality dMRI sequences require specific hardware and longer scanning sessions. Acquiring scans from patients after surgery is not straightforward given stimulation and MRI device restrictions as well as metal artifacts of leads and extensions (12,13). Moreover, processing of individualized dMRI data – especially when pooling across heterogeneous datasets – requires careful attention to reliability and confounders introduced by MR hardware and acquisition protocols (see (14) for a more detailed critical analysis). The main issue remains, however, that individualized brain connectivity data in DBS is scarcely available, even world-wide.

The use of *normative connectomes* or manually curated *normative pathway atlases* addresses some of these limitations providing critical data on the relationships between stimulation sites, brain connectivity and clinical outcomes. However, we emphasize that these datasets represent *atlases* of average brain connectivity. In the case of diffusion-MRI derived atlases, the same problem of high false-positive rates of connections arises common to individual dMRI tractography datasets. In addition, these atlases do not bear any information about patient-specific anatomy. However, potential advantages may be seen in data quality. For instance, some diffusion MRI derived connectomes have been calculated from 1,000 subjects and acquired in specialized centers using specialized hardware (15–17). They could alternatively be derived from postmortem datasets that allow scanning times that would be unthinkable in vivo (18) or based on histology (5) and expert anatomical knowledge (6). Hence, the *ideal* data quality of connectome atlases will always be superior to the *ideal* individualized data set, in-vivo (7). But, critically, they will always be limited by patient-specific variations of anatomy (9). For OCD, both individual (19) and normative connectomes (15,20–22), as well as combinations of them (23), have been employed to study optimal connectivity profiles for DBS. Furthermore, first studies have *combined* the information available from normative (dMRI based) connectomes *and* histology based expert tract atlases (15,24).

We conclude that connectomic properties of DBS can yield important additional information about broader networks responsible for clinical effects. However, a consensus on which approaches work best and should be applied going forward is lacking. Direct head-to-head comparison studies would be useful to reach such a consensus, going forward. Objectives could be to study normative vs. individualized connectomes (14,23) (or both combined, for a discussion see (7)), fibers vs. voxels,

choice of tractography algorithms and measures of connectivity. Evidently, connectomic DBS highly depends on the validity of each incorporated assumption, i.e. the reconstruction of electrodes, modelling of electric field distributions and the appropriate connectivity estimate. Optimally, scientists could employ different complementary strategies (i.e. *optimal spot* analysis combined with *optimal network* analysis) and DBS models to ensure validity of their results.

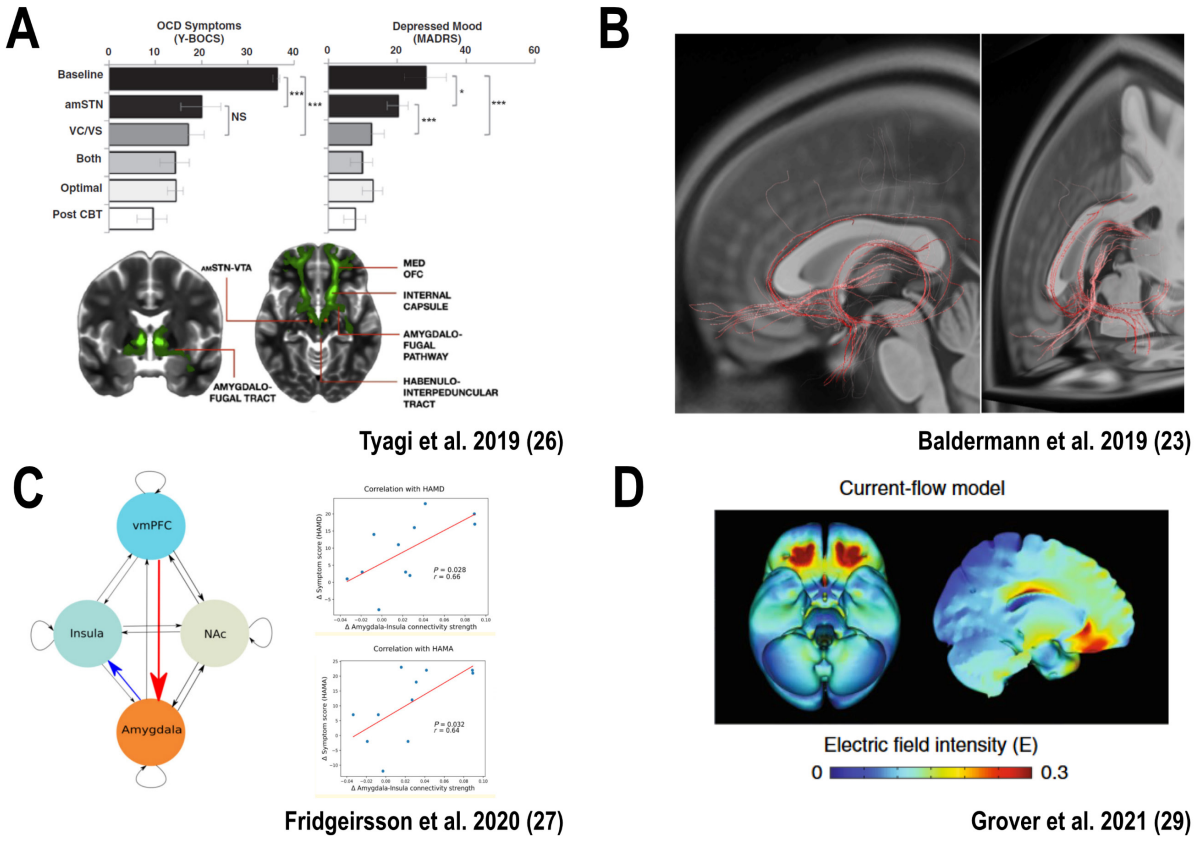

Figure S1: Evidence for a ventral reward/affect-related loop relevant for deep brain stimulation (DBS) in obsessive-compulsive disorder (OCD). A: A randomized controlled trial (26) targeting the anteromedial subthalamic nucleus (amSTN) and ventral capsule/ventral striatum target showed that the latter was more effective in reducing comorbid depression, while both target showed similar efficacy on OCD symptoms. B: A supplementary tractographic analysis by Baldermann et al. (23) showed that reductions in depressive symptoms after DBS of the anterior limb of internal capsule (ALIC) were associated with more ventrally located fibers connecting the ventromedial prefrontal cortex (vmPFC) and the subgenual cingulate cortex. C: Fridgeirsson et al. (27) revealed that switching (ALIC) stimulation off resulted in a dramatic increase in anxiety and depression, accompanied by changes in a functional network involving the vmPFC, amygdala, insula and nucleus accumbens D Grover et al. (29) demonstrated that cortical stimulation of the orbitofrontal cortex/vmPFC with transcranial alternating current resulted in a decrease of obsessive-compulsive symptoms in healthy adults, mediated by a reward related network. All panels reproduced, with permission, from original work as indicated. Panel A reproduced from Tyagi et al. 2019 (26) under the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0).

Text Box S1: Different approaches have been developed to study pathways associated with clinical response to DBS. A general discussion of the methodological approaches is given in the supplement. For a brief overview, the following methods have been used in patients with OCD:

Approach A) *Tract- / pathway-activation models* (TAM/PAM): This approach models individual axonal pathway activation (28) by placing axonal cable models alongside a priori defined and established anatomical fiber tracts. The axonal response of these pathways to DBS is then estimated based on electrode location and stimulation parameters. The resulting pathway profiles can then be assigned to clinical outcome of OCD (e.g. 25)

Approach B) *Spatial pathway dependency*: This method calculates spatial dependencies (e.g., *distance*) of stimulation sites or volumes of activated tissue (VATs) with predefined pathways from tractography. Clinical outcomes can then be assigned to the respective spatial dependency (e.g. 26).

Approach C) *Activation volume tractography* (AVT): Streamlines are filtered that traverse VATs as the seed region from either a finite set of tracts (24) or whole-brain connectomes (31). The resulting individual stimulation-dependent connectivity profiles can then be matched with clinical outcome for group analysis using the following approaches:

1) *DBS network modeling*: Assessment of voxel-by-voxel association of connectivity estimates and clinical outcome (e.g. regression analysis) (e.g. 29, 43)

2) *DBS Fiber filtering* or *discriminative tractography*: Assessment of a tract-by-tract analysis comparing outcomes of patients with and without a specific fiber tract modulation (15,20–23)

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