

Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases

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Brain stimulation, a therapy increasingly used for neurological and psychiatric disease, traditionally is divided into invasive approaches, such as deep brain stimulation (DBS), and noninvasive approaches, such as transcranial magnetic stimulation. The relationship between these approaches is unknown, therapeutic mechanisms remain unclear, and the ideal stimulation site for a given technique is often ambiguous, limiting optimization of the stimulation and its application in further disorders. In this article, we identify diseases treated with both types of stimulation, list the stimulation sites thought to be most effective in each disease, and test the hypothesis that these sites are different nodes within the same brain network as defined by resting-state functional-connectivity MRI. Sites where DBS was effective were functionally connected to sites where noninvasive brain stimulation was effective across diseases including depression, Parkinson's disease, obsessive-compulsive disorder, essential tremor, addiction, pain, minimally conscious states, and Alzheimer's disease. A lack of functional connectivity identified sites where stimulation was ineffective, and the sign of the correlation related to whether excitatory or inhibitory noninvasive stimulation was found clinically effective. These results suggest that resting-state functional connectivity may be useful for translating therapy between stimulation modalities, optimizing treatment, and identifying new stimulation targets. More broadly, this work supports a network perspective toward understanding and treating neuropsychiatric disease, highlighting the therapeutic potential of targeted brain network modulation.

human connectome project | neurosurgery | TMS | tDCS | clinical application

A promising treatment approach for many psychiatric and neurological diseases is focal brain stimulation, traditionally divided into invasive approaches requiring neurosurgery and noninvasive approaches that stimulate the brain from outside the skull. The dominant invasive treatment is deep brain stimulation (DBS) in which an electrode is surgically implanted deep in the brain and used to deliver electrical pulses at high frequency (generally 120–160 Hz) (1, 2). In some instances, the therapeutic effects of DBS resemble those of structural lesions at the same site, but in other cases DBS appears to activate the stimulated region or adjacent white matter fibers (1, 2). DBS systems are approved by the US Food and Drug Administration (FDA) for treatment of essential tremor and Parkinson's disease, have humanitarian device exemptions for dystonia and obsessive compulsive disorder, and are being explored as a therapy for many other diseases including depression, Alzheimer's disease, and even minimally conscious states (1, 3–6).

Although DBS can result in dramatic therapeutic benefit, the risk inherent in neurosurgery has motivated research into non-

invasive alternatives (7–9). Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have received the most investigation (10–13). TMS uses a rapidly changing magnetic field to induce currents and action potentials in underlying brain tissue, whereas tDCS involves the application of weak (1–2 mA) electrical currents to modulate neuronal membrane potential. Depending on the stimulation parameters, both TMS and tDCS can be used to excite (>5 Hz TMS, anodal tDCS) or inhibit (<1 Hz TMS, cathodal tDCS) the underlying cortical tissue (10). These neurophysiological effects are well validated only for the primary motor cortex (M1) and can vary across subjects; however the terms “excitatory” and “inhibitory” stimulation are used often and are used here as a shorthand to refer to TMS or tDCS at these parameters. The primary clinical application and FDA-approved indication is high-frequency (i.e., excitatory) TMS to the left dorsolateral prefrontal cortex (DLPFC) for treatment of medication-refractory depression (14–19). However, TMS and tDCS have shown evi-

Significance

Brain stimulation is a powerful treatment for an increasing number of psychiatric and neurological diseases, but it is unclear why certain stimulation sites work or where in the brain is the best place to stimulate to treat a given patient or disease. We found that although different types of brain stimulation are applied in different locations, targets used to treat the same disease most often are nodes in the same brain network. These results suggest that brain networks might be used to understand why brain stimulation works and to improve therapy by identifying the best places to stimulate the brain.

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Conflict of interest statement: M.D.F. is listed as inventor in issued patents or patent applications on functional connectivity and guidance of brain stimulation. A.M.L. receives research support from Medtronic, St. Jude Medical, and Boston Scientific; is a consultant for Medtronic and St. Jude Medical; serves on the scientific advisory board of Ceregene, Codman, Neurophage, Aleva, and Alcyone Life Sciences; is cofounder of Functional Neuro-modulation; and holds intellectual property in the field of Deep Brain Stimulation. A.P.-L. serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Allied Mind, Neosync, Magstim, Axilum Robotics, and Novavision and is listed as inventor in issued patents and patent applications on the real-time integration of transcranial magnetic stimulation with electroencephalography and MRI.

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Data deposition: MRI data is available for download from <http://neuroinformatics.harvard.edu/gsp>.

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dence of efficacy in a number of other neurological and psychiatric disorders (10–13).

How invasive and noninvasive brain stimulation relate to one another has received relatively little attention. Because of the different FDA-approved indications, patient populations, sites of administration, and presumed mechanisms of action, they have remained largely separate clinical and scientific fields. However, these boundaries are beginning to erode. First, the patient populations treated with invasive or noninvasive brain stimulation are starting to converge. For example, the primary indication for TMS is depression, and the primary indication for DBS is Parkinson's disease, but DBS is being investigated as a treatment for depression, and TMS is being investigated as a treatment for Parkinson's disease (4, 20–25). Second, although therapeutic mechanisms remain unknown, invasive and noninvasive brain stimulation share important properties. In both cases, the effects of stimulation propagate beyond the stimulation site to impact a distributed set of connected brain regions (i.e., a brain network) (4, 10, 26–33). Given increasing evidence that these network effects are relevant to therapeutic response (4, 34–36), it is possible that invasive and noninvasive stimulation of different brain regions actually modify the same brain network to provide therapeutic benefit.

Linking invasive and noninvasive brain stimulation and identifying the relevant brain networks is important for several reasons. First, findings could be used to improve treatments. For example, TMS treatment of depression is limited by the inability to identify the optimal stimulation site in the left DLPFC (15, 18, 37–39). Using resting-state functional-connectivity MRI (rs-fcMRI), a technique used to visualize brain networks based on correlated fluctuations in blood oxygenation (40–42), the efficacy of different DLPFC TMS sites has been related to their correlation with the subgenual cingulate, a DBS target for depression (43). rs-fcMRI maps with the subgenual cingulate thus might be used to select an optimal TMS site in the DLPFC, perhaps even individualized to specific patients (44). Because identification of the ideal stimulation site is a ubiquitous problem across diseases and brain-stimulation modalities (1, 15, 18, 37–39), such an approach could prove valuable across disorders. Second, although the primary goal of therapeutic brain stimulation is to help patients, it also can provide unique and fundamental insight into human brain function. Investigating how different types of stimulation to different brain regions could impart similar behavioral effects is relevant to understanding the functional role of brain networks.

Here we investigate all neurological and psychiatric diseases treated with both invasive and noninvasive brain stimulation. We list the stimulation sites that have evidence of efficacy in each disease and test the hypothesis that these sites represent different nodes in the same brain network as visualized with rs-fcMRI. Further, we determine whether this approach can identify sites where stimulation is ineffective and determine which type of noninvasive brain stimulation (excitatory or inhibitory) will prove effective. To test these hypotheses, we take advantage of a unique rs-fcMRI dataset collected from 1,000 normal subjects, processed to allow precise subcortical and cortical alignment between subjects and with anatomical brain atlases (45–47).

Results

Our literature search revealed 14 different psychiatric or neurological diseases with published reports of efficacy for both invasive and noninvasive brain stimulation (Table 1). For each disease, DBS targets were used as seed regions for rs-fcMRI analysis (*Experimental Procedures* and Fig. 1). Correlations between DBS seed regions and all other brain voxels were computed and related to sites with evidence of efficacy as targets for noninvasive brain stimulation. For example, the subgenual cingulate, the primary DBS target in depression, is negatively correlated with the DLPFC, the primary TMS target for depression (Fig. 1). We repeated this process for each of the 14 brain diseases, initially focusing on the sites of invasive and noninvasive brain stimulation that had the best evidence of efficacy in each disease (Fig. 2).

Qualitatively, the sites of effective DBS tended to be correlated (positively or negatively) with the sites of effective noninvasive stimulation across each of the 14 diseases (Fig. 2). To quantify this impression and to determine whether this association was significant, we compared the average correlation value underlying each noninvasive stimulation site with the values obtained from 372 similar but randomly distributed sites across the brain surface (*Experimental Procedures*). In 13 of the 14 diseases (all except epilepsy) the best site for DBS was significantly more correlated or anticorrelated with the best site for noninvasive stimulation than with random sites (Fig. 3A, black bars, $P < 0.001$). Because many diseases have more than one site at which invasive or noninvasive stimulation shows evidence of efficacy (Table 1), and indeed the “best site” can be debatable, we repeated the analysis, including all stimulation sites. The link between the sites of invasive and noninvasive brain stimulation remained signifi-

Table 1. Diseases with evidence of efficacy for both invasive and noninvasive brain stimulation and the stimulation targets

Disease	Target for invasive stimulation (DBS)	Target for noninvasive stimulation (TMS, tDCS)	References
Addiction	NA	DLPFC (laterality unclear)	(163–167)
Alzheimer's disease	Fornix	Bilateral DLPFC (\pm parietal, temporal)	(5, 83, 156, 168, 169)
Anorexia	NA, subgenual	Left DLPFC	(170–174)
Depression	Subgenual, VC/V5, NA, MFB, habenula	Left DLPFC, <i>right DLPFC</i>	(4, 14, 18–21, 24, 25)
Dystonia	GPI	<i>SMA/ACC, premotor</i>	(22, 175–177)
Epilepsy	Thalamus (AN, CM), MTL	<i>Active EEG focus, cerebellum</i>	(178–183)
Essential tremor	VIM	<i>Midline cerebellum, lateral cerebellum, M1</i>	(2, 53, 55, 56)
Gait dysfunction	PPN	M1 (leg area)	(66, 184–186)
Huntington's disease	GPI	SMA	(187, 188)
Minimally conscious	Thalamus (intralaminar/CL, CM/Pf)	Right DLPFC, M1	(6, 189–191)
Obsessive compulsive disorder	VC/V5, NA, ALIC, STN	<i>Left orbitofrontal, pre-SMA</i>	(192–198)
Pain	PAG, thalamus (VPL/VPM)	M1	(61, 152, 199)
Parkinson's disease	STN, GPI	M1, SMA	(2, 22, 23)
Tourette's syndrome	Thalamus (CM/Pf), GPI, NA, ALIC	SMA	(200–202)

Italics indicate targets of inhibitory rather than excitatory noninvasive stimulation. ACC, anterior cingulate cortex; ALIC, anterior limb of the internal capsule; AN, anterior nucleus; CL, central lateral nucleus; CM, central median nucleus; DLPFC, dorsal lateral prefrontal cortex; GPI, globus pallidus pars internus; M1, primary motor cortex; MFB, medial forebrain bundle; MTL, medial temporal lobe; NA, nucleus accumbens; PAG, periaqueductal gray; Pf, parafascicular nucleus; PPN, pedunculopontine nucleus; SMA, supplementary motor area; STN, subthalamic nucleus; VC/V5, ventral capsule/ventral striatum; VIM, ventral intermediate nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

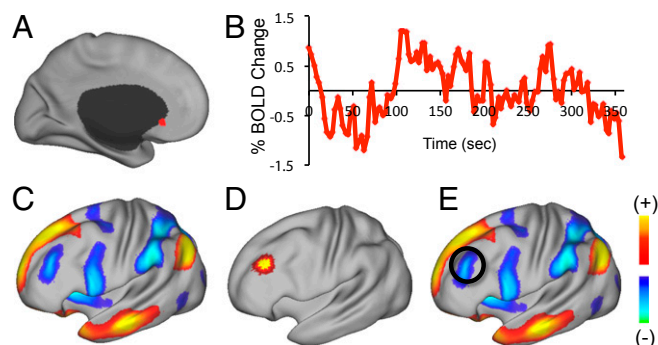


Fig. 1. Methodological approach for linking sites for invasive and non-invasive brain stimulation. (A) An ROI is created at a DBS site with reported efficacy for a given disease, in this case the subgenual cingulate for depression. (B) For each of 1,000 normal subjects, spontaneous modulations in the fMRI signal are extracted from this DBS ROI. (C) This time course is correlated with all other brain voxels and then averaged across subjects to create a DBS correlation map. (D) An ROI is created at the site where noninvasive stimulation is reported effective in the given disease, in this case the left DLPFC. (E) The site of noninvasive brain stimulation is illustrated on the DBS correlation map using a circle centered over the site.

cantly greater than chance in 10 of the 14 diseases (Fig. 3A, gray bars, $P < 0.01$). In addition to computing statistics within each disease, we also computed statistics across the 14 diseases (Fig. 3B). Across diseases, DBS sites showed significantly stronger functional connectivity to the sites where noninvasive brain stimulation was effective than to random sites, regardless of whether one considered only the best sites for stimulation in each disease (Fig. 3B, black bar) or all sites with evidence of efficacy (Fig. 3B, gray bar).

Next we investigated whether the sites where brain stimulation was ineffective were characterized by a lack of functional connectivity. To do so, we considered diseases in which a specific brain-stimulation site had been reported to be ineffective. For example, multiple randomized, controlled trials in Parkinson's disease have found that noninvasive stimulation to the left DLPFC fails to show significant motor improvements similar to those seen with noninvasive stimulation to M1 (48–52). Consistent with these findings, the Parkinson's DBS site in the subthalamic nucleus (STN) showed strong connectivity to M1 but not to the left DLPFC (Fig. 4A). In fact, connectivity between the STN and left DLPFC was less than the connectivity between the STN and random sites (Fig. 4A, graph). In other diseases, evidence that a specific site of noninvasive stimulation is ineffective is not as strong; however, in general, stimulation of cerebellum appears to be more effective for essential tremor than stimulation of M1 (53–57), stimulation of M1 appears to be more effective for pain than stimulation of DLPFC (58–61), and stimulation of the left DLPFC appears to be more effective for depression than stimulation of the cranial vertex (top of the head) (17). In all cases, the DBS site with the best evidence of efficacy was significantly more connected to the sites where noninvasive stimulation was effective than to sites where noninvasive stimulation was ineffective, with connectivity to the ineffective site falling at or below the connectivity to random sites (Fig. 4A–D).

One might use a similar strategy to predict whether DBS will be effective or ineffective at particular sites. For example, in Parkinson's disease DBS to the ventral intermediate nucleus (VIM) has been used for tremor but generally is ineffective for other motor symptoms such as bradykinesia and rigidity (2). These symptoms do respond to DBS of the STN or globus pallidus pars interna (GPI) as well as to noninvasive stimulation of M1 (22, 62). Consistent with this dissociation, there was strong functional connectivity between M1 and both the STN and GPI but not the VIM (Fig. 4E).

An important question is whether the sign of DBS functional connectivity (i.e., positive or negative correlation) relates to whether excitatory or inhibitory noninvasive stimulation is more effective. For example, both M1 and the supplementary motor area (SMA) are targets for noninvasive brain stimulation in Parkinson's disease but show a double dissociation regarding the type of stimulation found to be effective (Fig. 5A). Excitatory stimulation to M1 results in an improvement in Parkinson's scores (50, 63–66), but inhibitory stimulation shows little effect (63, 64, 67). In contrast, inhibitory stimulation to the SMA appears to improve scores (23, 68, 69), but excitatory stimulation leads to no effect or even to a worsening of symptoms (23, 68, 70). The opposite sign of the DBS correlation to these sites mirrored the opposite effects of excitatory and inhibitory noninvasive stimulation.

Across all diseases, sites at which inhibitory noninvasive stimulation was beneficial tended to be positively correlated with the DBS site, but sites at which excitatory stimulation was beneficial tended to be negatively correlated. This difference between sites of inhibitory and excitatory noninvasive stimulation was significant ($P < 0.005$), regardless of whether one considered only the sites in each disease where stimulation was most effective (Fig. 5B) or all sites with reported efficacy (Fig. 5C).

Finally, we performed several supplementary analyses to explore potential caveats of the above findings. Because rs-fcMRI results and particularly anticorrelations can depend on processing methods (71–75), we replicated our findings using an alternative approach that avoids the mathematical constraints associated with global signal regression (74) (Fig. S1). To ensure that results were not dependent on the clinical data from any particular disease, we randomly omitted any three diseases from the group of 14 and

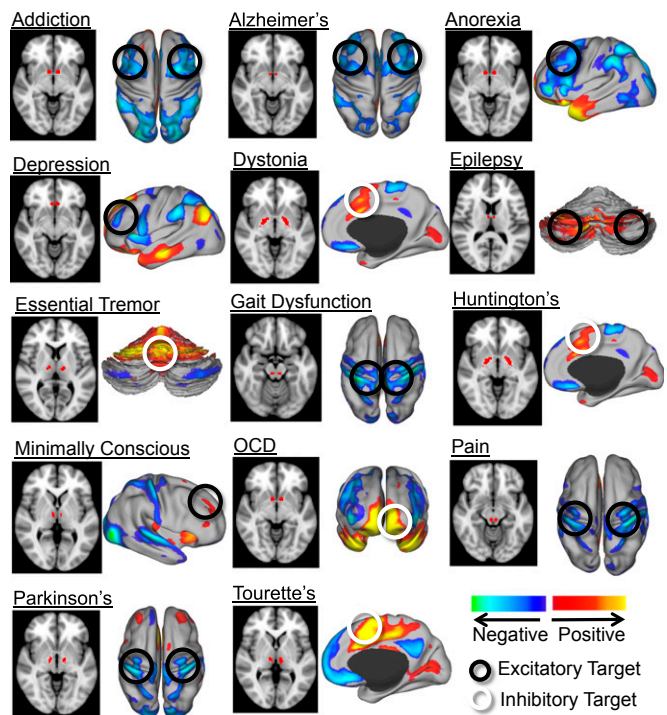


Fig. 2. Sites for invasive and noninvasive brain stimulation with the best evidence of therapeutic efficacy in each disease are functionally connected. For each disease, the site at which DBS is most effective is shown in red. Resting-state functional connectivity with this site is shown along with the correspondence to the site at which noninvasive stimulation is most effective in each disease (circles). Black circles indicate sites at which noninvasive excitatory stimulation (>5 Hz TMS or anodal tDCS) has been reported to be efficacious. White circles indicate sites where inhibitory stimulation (<1 Hz TMS or cathodal tDCS) has been reported to be efficacious.

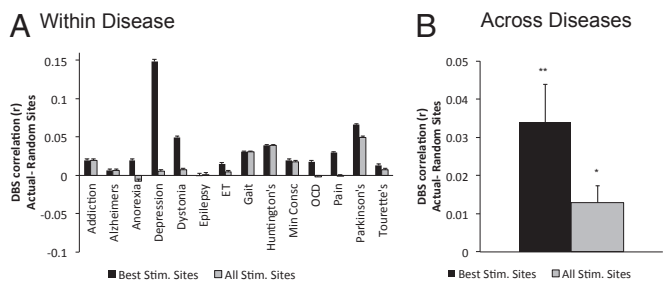


Fig. 3. Resting-state functional connectivity between sites of invasive and noninvasive brain stimulation is significantly higher than expected by chance. (A) For each disease, functional connectivity between the sites at which invasive and noninvasive stimulation are most effective is shown minus the connectivity between the same DBS site and random noninvasive sites (black bars). This analysis was repeated including all stimulation sites with evidence of efficacy rather than just the best site in each disease (gray bars). (B) Across diseases, resting-state functional connectivity between the site where DBS is most effective and the site where noninvasive stimulation is most effective (black bar) or between all sites where stimulation was effective (gray bar) was significantly greater than DBS connectivity with random sites. * $P < 0.01$, ** $P < 0.005$.

found that the relationship between the best sites for invasive and noninvasive brain stimulation remained significant at the group level ($P < 0.05$). To explore whether the rs-fcMRI results in 1,000 healthy subjects would be relevant to patient populations, we replicated our analyses in 56 patients with Parkinson's disease (Fig. S2) (76) and in 23 patients with medication-refractory depression presenting for TMS (Fig. S3). Finally, because activation of specific white matter tracks has been shown to be important for DBS effects in the subgenual cingulate (77–79), the VIM nucleus of the thalamus (80–82), and the fornix (5, 83), we explored anatomical connectivity with these sites using diffusion tractography and compared those results with the present findings with rs-fcMRI (Fig. S4). We found convergent anatomical and functional connectivity from the subgenual cingulate to the medial prefrontal cortex, from the VIM nucleus to the cerebellum and motor regions (the SMA and premotor), and from the fornix to memory regions (hippocampus and retrosplenial cortex).

Discussion

This article links sites of invasive and noninvasive brain stimulation across neurological and psychiatric diseases by identifying resting-state brain networks. Sites effective for the same disease tend to fall within the same brain network, ineffective sites fall outside this network, and the sign of network correlation appears to be relevant for determining whether excitatory or inhibitory noninvasive stimulation is more effective. These results motivate a network perspective on brain stimulation that is relevant for understanding mechanisms of action and generating testable hypotheses regarding improving and optimizing therapy.

Identifying Stimulation-Related Brain Networks. Psychiatric and neurological diseases are increasingly conceptualized as diseases of brain networks, and network considerations have motivated the selection of many brain stimulation targets (34, 84–87). For example, the STN, GPi, M1, and SMA were chosen as stimulation targets in Parkinson's disease in part because they are part of the network of brain regions implicated in movement. As such, one could argue that the finding that different sites for therapeutic brain stimulation are part of the same brain network is expected and perhaps even trivial. However, how one defines and visualizes these networks is not straightforward, and predicting functional relationships relevant for therapeutic brain stimulation is difficult. For example, the STN is connected anatomically to both M1 and the SMA (88), so how does one predict that the motor symptoms in Parkinson's disease would respond differently to noninvasive

stimulation at these two sites? The subgenual cingulate lacks prominent direct anatomical connections to the DLPFC (89, 90), so how does one determine whether these sites are part of a single network that is relevant to depression? Finally, after defining and identifying stimulation-related brain networks, determining whether network properties transcend individual diseases and might guide application in other disorders is nontrivial.

Many techniques are potentially useful for investigating the brain networks associated with brain-stimulation sites. Here we focus on rs-fcMRI for both theoretical and practical reasons. From the theoretical standpoint, interactions observed with rs-fcMRI are sensitive to the influence of polysynaptic connectivity (40, 41, 91, 92). This sensitivity allows the identification of distant and complex network interactions that match well with data suggesting that the effects of brain stimulation are also polysynaptic (4, 10, 26–33). From the practical standpoint, prior work has used rs-fcMRI to predict the propagation of brain stimulation (93–95), link sites of invasive and noninvasive stimulation in depression (43), and identify biomarkers of the response to therapeutic brain stimulation (36). Moving forward, rs-fcMRI has potential as a clinical tool (42) and is robust enough to identify reproducible, individualized stimulation targets (44).

However, like any technique, rs-fcMRI has important limitations and caveats that must be recognized. First, although both rs-fcMRI and brain stimulation are polysynaptic, they do not necessarily reflect the same polysynaptic phenomena, and discrepancies exist (93–95). More advanced rs-fcMRI processing techniques designed to predict the influence of one region on another may prove better for identifying stimulation-based brain networks (96–98). Second, although there is a strong relationship between rs-fcMRI and anatomical white matter connectivity,

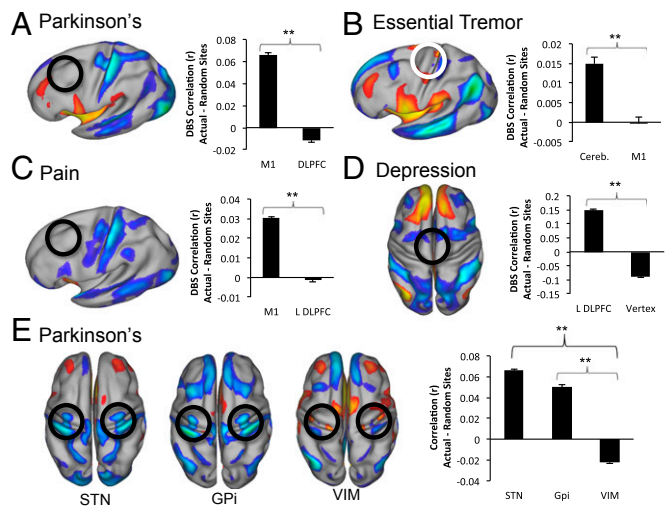


Fig. 4. Resting-state functional connectivity differentiates sites where brain stimulation is effective from sites where it is ineffective. (A–D) Diseases in which a specific site of noninvasive brain stimulation has been reported to be ineffective. For each disease, there is a lack of resting-state functional connectivity between the best DBS site for that disease and the site where noninvasive brain stimulation is ineffective (circle). In all cases, connectivity with the ineffective site was at or below chance levels and was significantly less than connectivity with the site at which noninvasive brain stimulation was effective for that disease (graphs). (E) One disease, Parkinson's disease, in which a specific DBS site (the VIM) has been found to be ineffective for most symptoms. Resting-state functional connectivity between the site where DBS is ineffective and the site where noninvasive brain stimulation is most effective (M1) was below chance and was significantly less than the connectivity between M1 and the sites where DBS was effective (graph). Black circles denote sites of excitatory noninvasive stimulation. White circles indicate sites of inhibitory noninvasive stimulation, as in Fig. 2. ** $P < 0.0001$.

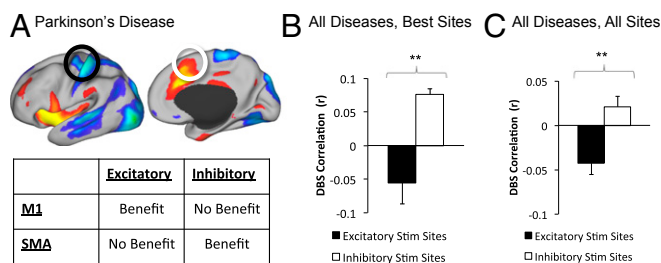


Fig. 5. Positive versus negative resting-state functional connectivity with DBS sites relates to whether excitatory (>5 Hz TMS or anodal tDCS) or inhibitory (<1 Hz TMS or cathodal tDCS) noninvasive brain stimulation has been found to be more beneficial. (A) Resting-state functional connectivity with the STN shows negative correlation with M1 (black circle) and positive correlation with the SMA (white circle), consistent with the double dissociation in clinical benefit seen with excitatory versus inhibitory noninvasive brain stimulation at these sites (table). (B and C) Across diseases, sites at which inhibitory noninvasive brain stimulation was reported to be beneficial were more likely to be positively correlated with the DBS site; sites at which excitatory stimulation was reported to be beneficial were more likely to be negatively correlated. Results are shown for the best stimulation sites in each disease (B) and for all stimulation sites (C). $^{***}P < 0.005$.

there are important differences (91, 99–101). This difference is relevant to the present investigation, because some DBS targets are white matter structures, and in several cases activation of specific white matter tracks has been related to clinical DBS response (32, 77–82, 102, 103). In these cases, we found convergence between anatomical connectivity measured with diffusion tractography and positive correlations measured with rs-fcMRI (Fig. S4) (77–82, 104). Perhaps surprising are the rs-fcMRI correlations between the fornix, a white matter structure, and distant memory regions including the hippocampus and retrosplenial cortex (Fig. S4C). rs-fcMRI clearly is better suited for investigating gray-matter targets; however white matter does contain a small fMRI signal that has been used for activation and rs-fcMRI mapping (105–108). Future work integrating the complementary strengths of diffusion-based tractography and rs-fcMRI is likely to prove valuable. We did not attempt to relate anatomical connectivity to rs-fcMRI anticorrelations, because doing so would require complicated modeling beyond the scope of the present investigation (109–111). However, such models suggest that anticorrelations emerge as a functional consequence of multiple indirect anatomical connections and temporal delays (109–111). Ongoing advances in hardware and software are likely to improve upon these anatomy-based models further and soon may predict the present rs-fcMRI relationships as well as brain-stimulation effects (91, 112–114).

In addition to the above caveats, rs-fcMRI has smaller technical limitations that deserve mention. The processing approaches used to eliminate global signal fluctuations have a significant impact on observed anticorrelations (71–75). It is important that our results remained significant with two different processing strategies; however, further work is needed to determine the best approach to predict the results of brain stimulation. Second, the spatial resolution of rs-fcMRI is limited. Small changes in DBS electrode position below this resolution can have profound effects on clinical response that may limit the utility of rs-fcMRI (115–117). Finally, seed-based functional-connectivity results are highly dependent on the position of the seed region. To avoid bias, we defined seed regions based on published atlases or coordinates whenever possible (116, 118–120). However, effective DBS electrode contacts may lie outside the targeted neuroanatomical structure (e.g., ref. 115), and modeling the volume of tissue affected by DBS is non-trivial (116, 121). Similarly, regions of interest (ROIs) representing sites of noninvasive brain stimulation often had to be approximated based on clinical descriptions and scalp landmarks and used a rel-

atively simple model of tissue activation (44, 122, 123). We hope that this article and others like it will encourage the use of neuro-navigation in future TMS clinical trials, improving our ability to relate brain-stimulation sites to brain networks.

One final feature of our approach that should be highlighted is that for most analyses we used rs-fcMRI data from a large cohort of normal subjects, not data from patients. The finding that rs-fcMRI patterns in normal subjects relate to clinical outcome data from patients builds on prior work showing that rs-fcMRI patterns in normal subjects predict disease patterns in patients (86, 124). These results are important in suggesting that large normative datasets could be used to guide therapy in patients, potentially representing a direct therapeutic application of the Human Connectome Project (125). Although such normative group-level targeting of brain stimulation may be valuable, additional benefit could come from targeting based on rs-fcMRI in patients and perhaps even individualized to specific patients (44). As such, it is reasonable to ask whether our results in normal subjects would hold true in disease populations, given that rs-fcMRI is known to be abnormal in different disease states (42, 126). Although differences in the cohorts were present, for the most part our results in normal subjects were replicable in patients with Parkinson's disease and medication-refractory depression (Figs. S1 and S2). These results are consistent with prior findings suggesting that disease represents a deviation in the normal connectivity pattern but generally not a completely different pattern (for examples, see refs. 43, 127, and 128). Whether connectivity from normative databases, groups of patients, or individual patients will prove most informative in understanding and targeting brain stimulation requires further work.

Brain Diseases Treated with both Invasive and Noninvasive Stimulation.

We provide a comprehensive list of brain conditions across psychiatry and neurology in which there is evidence of efficacy for both invasive and noninvasive stimulation (Table 1). However, this list is intended as a resource to guide research and should not be interpreted as a formal meta-analysis or evidence of proven clinical efficacy. Recently, for example, two multisite trials of promising DBS targets for depression were halted for futility (25). Determining why these results differ from prior findings and incorporating data from ongoing trials will be necessary before definitive statements on clinical efficacy can be made. Importantly, the goal of this article is not to evaluate the clinical efficacy of any particular brain-stimulation target but to synthesize existing brain-stimulation data across modalities and diseases in a way that allows new insights and testable hypotheses. That our primary finding remains significant after the random omission of any three of the 14 diseases suggests that it will be rather robust to negative results from any given trial.

Although invasive and noninvasive brain stimulation are being used increasingly to treat patients with the same diagnosis, the patient cohorts are not necessarily the same. Patients treated with DBS generally are more severely afflicted and treatment refractory than those treated with noninvasive stimulation, raising the question of whether they share the same pathophysiology. Whether patients with the same disease severity will respond equally well to different types of brain stimulation at different network nodes is an important topic for future investigation.

Our study was limited to DBS, TMS, and tDCS; however, other brain-stimulation techniques deserve mention. Invasive cortical stimulation involves the surgical implantation of an electrode on the surface of the brain. The current results are likely to be pertinent to this technique, because the sites of cortical implantation tend to be the same targets used for noninvasive stimulation, including M1 in Parkinson's disease (129, 130), M1 in essential tremor (54), premotor cortex in dystonia (131), left DLPFC in depression (132), cerebellum in epilepsy (133), and M1 in pain (61). Other noninvasive brain-stimulation modalities include electroconvulsive therapy and vagal nerve stimulation, which show therapeutic effi-

cacy but are not applied to a specific brain location, and techniques for which therapeutic investigation is ongoing, such as focused pulsed ultrasound, magnetic seizure therapy, and light-stimulation therapy. The relevance of the current results to these other non-invasive brain-stimulation modalities remains to be determined.

Insight into the Therapeutic Mechanisms of Brain Stimulation. The mechanism of action for both invasive and noninvasive brain stimulation remains a matter of intense investigation and significant debate (1, 2, 10–12, 33). The current finding that both types of stimulation impact nodes in the same network supports a growing belief that network-level effects may be as important as local effects in understanding the therapeutic response (1, 10, 33, 35). An important question is how different types of brain stimulation with complex neurophysiological effects applied to different nodes of a network could impart similar symptomatic benefit. Here we highlight four possibilities. First, symptoms could be caused by activity in one region, and stimulation at other nodes could propagate through anatomical connections to impact this region (4, 10, 26–33). Second, symptoms could be caused by the balance of activity between brain regions, rather than by activity in a single region, so that stimulation of multiple different regions could modify this balance (4, 35). Third, symptoms could be caused by abnormal connectivity within a brain network, and stimulation of any node of this network could alter such connectivity (35, 42, 126, 134–139). Finally, symptoms could be caused by pathological oscillations occurring within a network, and stimulation of any node of the network could break this pathological rhythm (33, 140–144).

These various mechanisms of network modulation are by no means mutually exclusive, and different mechanisms may explain the different time scales over which therapeutic responses can occur (1). For example, breaking abnormal oscillations may underlie the immediate impact of DBS on tremor, whereas changes in network connectivity could underlie the delayed effect of DBS on dystonia or TMS on depression (36).

Implications for Targeting Therapy. Guiding noninvasive stimulation based on invasive stimulation. One of the most important practical implications of the present work is a testable method for translating the success of DBS into new and improved noninvasive treatments. For example, the current FDA-approved approach for targeting TMS to the DLPFC for the treatment of depression is to stimulate a spot 5 cm anterior to the motor cortex along the curvature of the scalp (14–17). It is not surprising that this technique leads to variability in both the stimulated region and therapeutic response (15, 18, 37–39). Despite widespread recognition of this problem, there was no clear neurobiological basis upon which to base a better targeting alternative. The promising success of DBS to the subgenual cingulate in the same disease (4, 145) suggests that connectivity with the subgenual could help refine target selection in the DLPFC (43, 44). In a similar manner, connectivity with other DBS sites may help refine targets at other TMS nodes.

Beyond refining targets, DBS connectivity may help identify completely new targets. For example, subgenual connectivity suggests that TMS to the parietal cortex may have an antidepressant effect similar to that seen with TMS to the DLPFC (146, 147). Similarly, connectivity with the nucleus accumbens suggests that lateral orbitofrontal cortex may be a useful stimulation target for addiction and compulsions, a suggestion that is consistent with recent evidence from animal models (148).

Guiding invasive stimulation based on noninvasive stimulation. One also can invert this strategy and use distributed cortical sites or networks to identify an ideal site for DBS. For example, rs-fcMRI with motor and cerebellar networks identifies foci near the VIM and has been suggested as a guide for DBS in essential tremor (149). The practical utility of this approach may depend on improved spatial resolution and rs-fcMRI processing techniques. However, even at its current resolution, rs-fcMRI may prove

valuable in determining which nucleus to pursue in the first place. For example, trials for DBS in pain have produced heterogeneous results, and in fact pain (or, at least, trigeminal neuralgia) is one condition in which noninvasive brain stimulation may have better efficacy than DBS (61). In theory, one could examine connectivity with sites of effective or ineffective noninvasive stimulation in M1 to identify candidate DBS sites for different aspects of pain.

Another way in which noninvasive brain stimulation could guide DBS is to allow preoperative piloting of the impact of invasive stimulation. For example, there is some evidence that TMS to M1 may predict the effect of surgically implanted epidural electrical stimulation (150). One could imagine stimulating cortical patterns reflecting the STN versus the GPi to indicate which nucleus should be targeted in a given patient with Parkinson's disease (151). Even more valuable could be stimulating patterns associated with different experimental DBS targets to determine which DBS site should be pursued in a clinical trial.

Multifocal stimulation. A network perspective on brain stimulation suggests that multiple different sites can serve as nodes to influence a given network and raises the question of whether additional benefit could be obtained by treating multiple sites. Multifocal DBS has been used in pain and Parkinson's disease (152, 153), multifocal TMS has been used in Parkinson's disease and Alzheimer's disease (154–156), and the excitatory/inhibitory effect of the two tDCS electrodes has been used in stroke recovery (157). Moving beyond two sites, the DBS correlation maps presented here identify entire cortical patterns that potentially could be stimulated or inhibited with multifocal TMS (158, 159) or multifocal tDCS arrays (160). In fact, algorithms recently have been developed that generate tDCS arrays designed to match a given cortical pattern optimally, including patterns based on rs-fcMRI with effective sites for DBS (160).

Conclusions

Across psychiatric and neurological diseases, sites for invasive and noninvasive brain stimulation fall within the same brain network, as defined by rs-fcMRI. Such findings have implications for understanding brain stimulation as a network phenomenon and generate specific hypotheses regarding optimization of brain-stimulation therapy that can be tested in future clinical studies.

Experimental Procedures

Diseases or conditions with published reports suggesting efficacy of both DBS and a noninvasive brain-stimulation modality (TMS or tDCS) were identified via a PubMed search with predefined search criteria. For each stimulation target, an ROI was created based on existing atlases or neuroanatomical coordinates (118). Noninvasive stimulation targets were modeled as spheres with a 12-mm radius of graded intensity (44). ROI coordinates and associated references are available for each target of invasive (Table S1) and noninvasive (Table S2) stimulation. Each DBS ROI was used as a seed region in a seed-based rs-fcMRI analysis (40) using a previously published rs-fcMRI dataset of 1,000 normal subjects (47). MRI data were processed with a combination of nonlinear volumetric warping and surface registration to allow precise subcortical and cortical alignment (45, 46). Processing involved removal of confounding variables, including global signal regression (161); an alternative strategy avoiding global signal regression was used also (74, 162). For each resulting DBS correlation map, the average voxel value underlying each noninvasive stimulation site was computed and compared statistically with the values underlying 372 random sites scattered across the brain surface.

Additional methodological details are given in *SI Experimental Procedures*.

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