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Translation of network mapping findings into therapeutic targets for transcranial magnetic stimulation

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ABSTRACT

Transcranial magnetic stimulation (TMS) has been used to effectively treat certain brain disorders, such as major depressive disorder, and holds great promise for other neurological and psychiatric symptoms. However, despite the increase in the number of trials conducted, the discovery of novel clinical applications of TMS has been limited. A key limiting factor is the absence of a priori methods capable of reliably localising symptom-specific targets in the brain that will respond to TMS. Network mapping methods have taken a different approach to prior neuroimaging techniques by mapping the structural or functional connections of brain abnormalities (e.g. locations of causal lesions or brain atrophy) to identify brain networks commonly connected to these focal abnormalities. Retrospective analyses have demonstrated overlap with current targets for clinical neuromodulation, and recently, studies have begun to prospectively target these networks with TMS. However, the translation of network mapping findings to TMS trials is not straightforward. The present review discusses how researchers can use the information provided by network mapping to help translate these findings to TMS trials, with an emphasis on target localisation. We first summarise the evidence for network mapping to identify targets for TMS, and then offer pragmatic guidance on target selection based on the on the nature of the network mapping results, feasibility and tolerability of TMS to the target, and considering the TMS electric field distribution in the brain. Overall, this review facilitates the translation of network mapping findings into novel targets for TMS trials in a range of brain disorders.

Introduction

Transcranial magnetic stimulation (TMS) is a widely used technique in research and clinical settings, capable of modulating brain network excitability to treat symptoms of psychiatric and neurological disorders (Polanía et al., 2018). TMS involves holding a plastic-coated wire coil over the scalp, where an electric current is transiently (<1 ms) passed through the coil, generating a time-varying magnetic field, in turn

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inducing a secondary electric field (e-field) in the underlying cortex (Klomjai et al., 2015). When applied repeatedly, TMS is capable of driving neuroplasticity in the targeted neural circuits, modulating the strength of cortico-cortical and cortico-subcortical connections (Bestmann et al., 2004). The ability of TMS to modulate neural circuits has led to a range of clinical applications. In contrast to other techniques used to modulate neural activity, such as deep brain stimulation (DBS) or ablative lesions, TMS does not involve surgery and has a very low incidence of serious side effects and adverse events (Rossi et al., 2021; Shafi, 2019). This makes TMS an attractive tool for therapeutic intervention, and particularly for pilot trials testing the therapeutic potential of new treatment targets.

The clinical efficacy of TMS was first shown through the treatment of pharmacoresistant major depressive disorder (MDD), after which the field anticipated novel TMS therapies would be developed and applied to treat a broad range of neurological and psychiatric disorders (Cohen et al., 2022; George, 2019). However, despite trials having been conducted for many different conditions, including Parkinson's disease (Zhang et al., 2022), pain (Attia et al., 2021), dystonia (Morrison-Ham et al., 2022), Alzheimer's disease (Zhang et al., 2025), and addiction (Antonelli et al., 2021), TMS is only in widespread clinical use for a select few brain disorders (Cohen et al., 2022). For example, since the clearance of TMS for MDD in 2008, the US FDA has only cleared TMS for four additional indications: migraine with aura, obsessive-compulsive disorder, smoking cessation, and anxiety comorbid with MDD (Cohen et al., 2022).

The discovery of novel clinical applications of TMS depends on the consideration of a large range of methodological parameters, such as dose, intensity, underlying brain state, possible concurrent therapies, and the personalisation of these factors to the patient. Yet a critical first step we have yet to properly resolve is the prospective localisation of targets in the brain that will alleviate symptoms when stimulated with TMS. Neuroimaging studies designed to localise neural structures driving neurological or psychiatric symptoms often produce heterogeneous findings (Button et al., 2013; Darby et al., 2019; Fox, 2018; Poldrack et al., 2017), therefore, we do not have pipelines that can reliably predict clinically effective TMS targets. One of the most exciting recent developments addressing this issue is that of 'network mapping' - a group of novel neuroimaging methods that can identify brain networks driving neurological and psychiatric symptoms (Darby et al., 2019; Fox, 2018; Joutsa et al., 2022; Tetreault et al., 2020). Network mapping differs from existing neuroimaging methods through its use of the human brain connectome to localise heterogeneously located brain abnormalities (e.g. brain lesions or focal atrophy) to a common brain network (for reviews, see Fox, 2018; Joutsa et al., 2022; Siddiqi et al., 2024). For instance, Joutsa et al. (2022) found lesions that preceded patients' smoking cessation were located in various brain areas but were characterised by a specific pattern of connectivity to the dorsal cingulate, lateral prefrontal cortex, and insula. To date, these network mapping methods have localised brain networks in over 40 neurological and psychiatric disorders, such as parkinsonism, hallucinations, and dystonia (Joutsa et al., 2022). One of the key stated implications of these studies is the potential for networks to be prospectively targeted using neuromodulation (e.g. DBS, TMS) (Butenko et al., 2025; Corp et al., 2019; Horn & Fox, 2020; Joutsa et al., 2022; Joutsa et al., 2022; Ríos et al., 2022; Younger et al., 2023), and several studies have used retrospective analyses to show that existing neuromodulation targets overlap with these networks (Cash et al., 2023; Ganos et al., 2022; Horn et al., 2025; Peng et al., 2022; Siddiqi et al., 2021).

Recently, studies have begun to test the therapeutic potential of network mapping findings by prospectively targeting these structures with TMS (ACTRN12621000417886; NCT04604210, Taylor et al., 2026; ACTRN12623001146684, Chen et al., 2025) and given the number of networks identified, more trials will likely be initiated in the coming years. However, the translation of these network mapping findings to testable targets for TMS is not straightforward and requires consideration of numerous factors. The aim of this review is to highlight how researchers can best use the information provided by network mapping to help translate these findings to TMS trials, with an emphasis on target localisation. First, we summarise current evidence for targeting network mapping findings with TMS, then discuss practical factors for researchers to consider when translating network mapping findings into TMS studies. These factors include: the selection of a target based on network mapping results, whether a proposed target is feasible and tolerable to stimulate, and considerations of the TMS electric field when defining a target site. By highlighting these considerations, we aim to bridge the gap between the fields of network mapping and TMS and promote the translation of network mapping results into novel testable targets for TMS clinical trials in a range of brain disorders. It is important to note that there are many other methodological factors to consider when designing a TMS trial (such as dose, intensity, brain state, etc.,), yet the present review specifically focuses on the above TMS factors that may be informed by network mapping findings. Therefore, while these other factors are also crucial to consider, they are outside the scope of the present paper and we refer readers to prior reviews for guidance on these issues (Siddiqi et al., 2024; Soleimani et al., 2024).

General overview of network mapping methods

Over the past ten years, various network mapping methods have been developed, each based upon using a human connectome to localise brain networks that may be driving symptoms in brain disorders (Fig. 1). Human connectomes can provide information about the brain's intrinsic structural and functional connections, in effect providing a 'wiring diagram' of the human brain (Elam et al., 2021). In this way, instead of analysing only an *anatomical location* of, for example, a brain lesion or site of focal atrophy, the connectome can be leveraged to map the neural networks commonly *connected* to these locations (Joutsa et al., 2022).

The first innovative application of this approach in a clinical cohort was with a technique called 'lesion network mapping' (LNM), which maps connectivity patterns from lesions that caused the same clinical outcome to identify a common underlying network. In this first use of LNM, Boes et al. (2015) demonstrated that, although lesions causing visual hallucinations were located throughout various anatomical locations, nearly all were functionally connected to the extrastriate visual cortex, suggesting that this region may be a hub of a distributed brain network driving visual hallucinations. While most LNM studies have examined lesions that *cause* symptoms, there are rare cases where lesions *relieve* symptoms, which have also been used in LNM studies to identify brain networks implicated in symptom relief (Joutsa et al., 2022; Joutsa et al., 2018). Studies have also used connectomes derived from diffusion-weighted imaging to map the white matter connections, that when intersected by a lesion, were associated with post-stroke behavioural deficits (e.g. (Billot et al., 2022; Kolskår et al., 2022; Salvalaggio et al., 2020; Thiebaut de Schotten et al., 2020). Most network mapping studies have used a normative human connectome because these are generally derived from a higher sample of participants (e.g., the 1000 healthy young adult rs-fMRI connectome (Holmes et al., 2015; Yeo et al., 2011)), increasing signal to noise ratio. However, some studies have also used connectomes specific to the disease under investigation (Horn et al., 2017; Joutsa et al., 2022). Generally, similar results have been shown using normative and disease-specific connectomes, yet this has not been demonstrated across all diseases, and these symptom-matched connectomes may become more utilised as sample sizes increase.

Since the development of LNM in 2015, several related network mapping methods have also emerged, including 'coordinate network mapping' (CNM; Darby et al., 2019), which maps connectivity from coordinates of structural brain abnormality reported in neuroimaging studies, and 'atrophy network mapping' (ANM; Tetreault et al., 2020) which maps connectivity of atrophy patterns from individual patients' MRI scans. More recently, a technique termed 'activation network

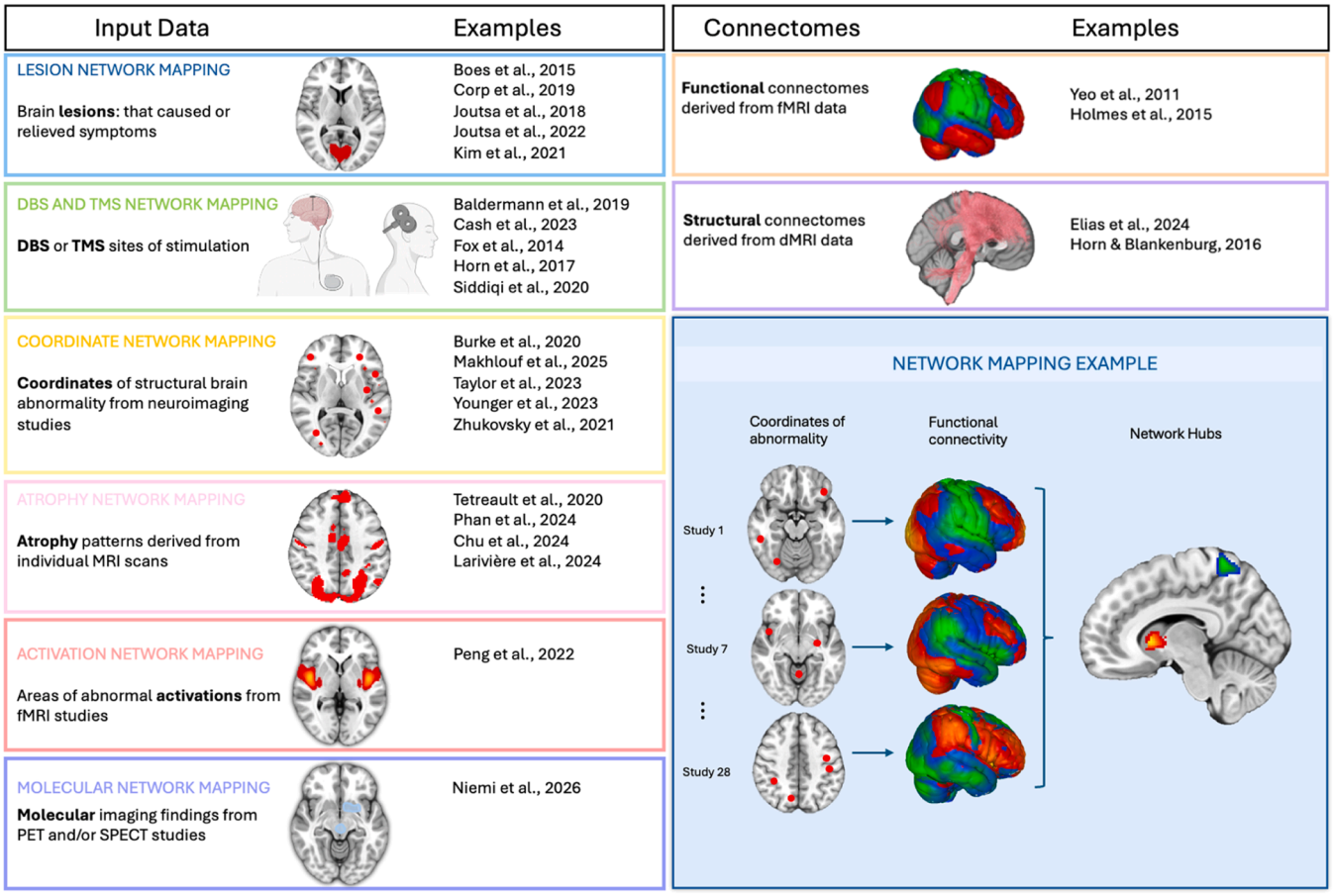

Fig. 1. Network Mapping Methods. Examples of input data used in network mapping analyses and example studies in which they have been used (left). Images shown are representations only and do not reflect actual data. Functional or structural connectomes are used in network mapping methods to investigate connectivity from input data; example connectome datasets are listed (top right). Images show example functional and structural connectivity patterns from an arbitrary seed. To demonstrate the concept of network mapping, an (fictional) example of the initial step of coordinate network mapping is shown in the bottom right, whereby functional connectivity is mapped from coordinates of brain abnormalities to identify commonly connected network hubs. Importantly, final brain networks are nearly always derived from additional analyses, such as 'specificity testing' (comparisons to connectivity patterns from control brain disorders), yet these are not visualised here. Figure created with BioRender. Younger, E. (2026) https://BioRender.com/e3ghjtg (Baldermann et al., 2019; Chu et al., 2024; Elias et al., 2024; Horn and Blankenburg, 2016; Joutsa et al., 2022; Kim et al., 2021; Lariviere et al., 2024; Makhlouf et al., 2025; Phan et al., 2024; Taylor et al., 2023; Zhukovsky et al., 2021).

mapping' has also been used which maps connectivity from areas of functional abnormality reported in functional magnetic resonance imaging (fMRI) studies (Peng et al., 2022), and similarly, the method of 'molecular network mapping' has leveraged molecular imaging findings from PET or SPECT studies, localizing them to brain networks using the same pipeline as LNM (Niemi et al., 2026). Additionally, 'TMS network mapping' and 'DBS network mapping' have been developed to identify structural and functional networks that are associated with clinical improvement from brain stimulation (Horn et al., 2017; Siddiqi et al., 2021). Fig. 1 provides a schematic of each of these 'network mapping' techniques.

It should be noted that the foundational methods of network mapping methods were recently challenged by demonstrating similarity between maps derived from different symptoms (van den Heuvel et al., 2026), and therefore whether network hubs could in fact represent novel symptom-specific targets for brain stimulation. However, the analyses of (van den Heuvel et al., 2026) did not reflect the methods generally used in network mapping approaches, in particular 'specificity testing', which is a critical step in all neuroimaging research, including network mapping techniques, to control for non-specific connectivity that is common across typical lesion locations investigated with a connectome. Numerous responses to this study have now been published, each demonstrating that network mapping techniques can identify symptom-specific networks (Petersen et al., 2026; Siddiqi et al., 2026; Wawrzyniak et al., 2026; Zalesky & Cash, 2026).

Examples of network mapping identifying known brain stimulation targets

Several studies using network mapping methods have localised brain networks that encompass existing brain stimulation targets. For example, LNM of lesions relieving tremor in essential tremor patients (Joutsa et al., 2018) and CNM of structural neuroimaging findings in essential tremor (Younger et al., 2023) both identified the ventral intermediate nucleus of the thalamus to be a key area of the essential tremor network, which is the most commonly used DBS target to relieve tremor (Horn et al., 2017). Other LNM studies have also identified brain networks that aligned with patterns of brain activity predicting therapeutic response to DBS, in disorders such as parkinsonism (Joutsa, Horn, et al., 2018), cervical dystonia (Corp et al., 2019) and tics (Ganos et al., 2022). In other words, these studies are proof-of-principle that network mapping techniques could have identified these effective stimulation targets, if they had not been already known.

Whilst these studies demonstrated networks aligning with DBS sites, other network mapping studies have localised networks that encompass existing TMS targets. For example, the CNM network of migraine

identified by Burke et al. (2020) overlapped with the field of TMS stimulation used for migraine treatment and so may point to a more a specific TMS target. More recently, Joutsa et al. (2022) demonstrated that lesions associated with smoking cessation (i.e., 'beneficial' lesions) were strongly connected to a network hub in the prefrontal and insular cortices. This network overlapped with the area stimulated in the approved TMS protocol for smoking cessation (Zangen et al., 2021). Importantly, Joutsa et al. (2022) suggested that these results could be used to refine the current deep-TMS target for addiction using the peaks of the network, which differed slightly to the original target site. Newer methods such as activation network mapping have also shown relevance to brain stimulation targeting, for example, Peng et al. (2022) used this method to identify a network of facial emotion processing, and demonstrated that although TMS targets disrupting this process were located in various brain areas, 11/13 target sites hit the identified network.

Network mapping methods are also being explored to improve brain stimulation in depression. (Padmanabhan et al., 2019) identified a lesion-derived depression circuit centred on the left dorsolateral prefrontal cortex, aligning with the existing TMS target, and Siddiqi et al. (2021) demonstrated that depressive networks derived by TMS network mapping, DBS network mapping and LNM were spatially similar. Recently, this depression network was supported in an independent sample, showing that multiple sclerosis patients with comorbid depression had a significantly higher lesion burden this network compared to patients without comorbid depression (Baller et al., 2024). In addition, Cash and colleagues (2023) demonstrated that divergent coordinates from task-based imaging research localised to statistically robust distributed brain networks implicated in emotional and cognitive dysfunction in depression, and importantly, the emotional dysfunction circuit for depression captured all existing DBS and TMS grey matter targets for depression (Cash et al., 2023). Moreover, when these networks were used as a template to define personalised TMS targets retrospectively in an independent dataset, TMS therapeutic outcome was dependent on how effectively this emotional dysfunction circuit was targeted (Cash et al., 2023). Several additional studies have demonstrated methods to personalise TMS targets, especially within the context of individualised functional connectivity patterns within depression patients (Lynch et al., 2024, 2022). These methods are largely outside of the scope of the present review, and we refer readers to these studies for further discussion.

Overall, network mapping studies identifying known brain stimulation targets demonstrates that these methods can identify neural structures that have a clinical response to neuromodulation, and provide opportunities to refine these existing targets to attempt to improve the efficacy of these protocols.

Examples of network mapping identifying new transcranial magnetic stimulation targets

Given the evidence that network mapping can identify existing targets, we are now moving toward using these techniques to identify new targets for brain stimulation. Recently, the first study to prospectively test target engagement and metabolic effects of TMS to a site specifically localised by LNM was conducted by Kokkonen et al. (2024). Investigators targeted MNI coordinates in the primary somatosensory cortex (S1), defined by a prior analysis of functional connectivity to brain lesions causing cervical dystonia (Corp et al., 2019). Results showed that a single session of continuous theta-burst stimulation (cTBS) significantly increased metabolism in the S1 (relative to sham) in the cervical dystonia group compared to healthy controls, and effects extended beyond the stimulation site to the brainstem (Kokkonen et al., 2024). These findings motivated a therapeutic trial of cTBS to the same site within the S1 in cervical dystonia (ACTRN12621000417886). Another clinical trial has recently been conducted by Taylor et al. (2026) using TMS to target two symptom-specific networks (dysphoric and anxiosomatic), derived from TMS network mapping, in individuals with comorbid MDD and anxiety (NCT04604210). Meanwhile, Chen and colleagues are conducting a pilot study using intermittent theta burst stimulation (iTBS) to target individualised cortical sites that have strong functional connectivity to a lesion network of anorexia nervosa (ACTRN12623001146684; Chen et al., 2025).

Practical steps and considerations for translating network mapping findings to TMS targets

Selecting a target for TMS based on different network mapping evidence

Findings from each network mapping technique have the potential to be translated into targets for TMS. However, as these methods derive networks from different sources, it is important to consider that they may each have different implications for TMS targeting. For example, DBS and lesions that directly precede the onset or relief of symptoms provide a causal link between those brain areas and the symptom (Joutsa et al., 2022). In contrast, CNM and ANM involve patterns of brain atrophy associated with symptoms, which may be causal, but could also be compensatory or incidental (Siddiqi et al., 2022). Different methods also relate to different aetiologies of disorders (e.g. idiopathic or lesion induced) and therefore may hold greater relevance for the corresponding patient populations. Therefore, choosing a network that has been implicated by various sources of evidence and is supported by a broader mechanistic understanding, may provide the strongest basis for therapeutic targeting (Siddiqi et al., 2022). This may include networks that have been validated using additional analyses, such as functional connectivity analyses within independent datasets or predictions of DBS efficacy in separate patient cohorts (Ellis et al., 2024).

Although there is some supporting evidence (Siddiqi et al., 2021; Younger et al., 2023), it is currently unknown whether networks implicated in symptom *presentation* (e.g. derived from causal lesions or brain atrophy), and networks associated with symptom *relief* (e.g. derived from beneficial lesions, DBS or TMS) localise to the same neural structures in all symptoms/disorders. For example, in two separate studies, Joutsa et al. (2022); Joutsa et al. (2018) localised neural networks functionally connected to lesions causing paradoxical relief of tremor, and addiction symptoms. This is an important distinction in methodology because, theoretically, networks derived from symptom relief could hold greater relevance for TMS therapy. While each of the above factors should be considered when translating network mapping findings to TMS targets, the clinical effects of brain stimulation to neural networks derived from any of these different methods are yet to be elucidated and is an open question to be tested in future TMS clinical trials.

Identifying cortical TMS targets for direct and indirect network neuromodulation

A number of network mapping studies have localised key network regions in cortical areas (e.g. Corp et al., 2019; Siddiqi et al., 2020) which can be easily stimulated with TMS and are now being used as targets in TMS clinical trials (as above, e.g. ACTRN12621000417886; NCT04604210; (Taylor et al., 2026). However, many network mapping studies implicate subcortical network hubs that are not reachable with standard TMS coils. Whilst there are some TMS protocols that use specific coils (e.g. H-coils) to target deeper regions of the brain, such as those used in smoking cessation (Joutsa et al., 2022; Zangen et al., 2021), targeting a deeper structure leads to reduced focality and co-activation of cortical regions (Gomez-Tames et al., 2020). Therefore, the focus of this review is the localisation/refinement of more focal targets, reachable with standard TMS coils (i.e. figure-of-eight). An alternative solution is to use TMS to target a subcortical network hub indirectly by stimulating a strongly connected cortical site (Doyle Gaynor et al., 2008). Indeed, there has been a recent rise in the use of

concurrent TMS-fMRI to evaluate the ability of TMS (single-pulse and repetitive protocols) to engage specific subcortical structures through their cortical connections (for a review see Bergmann et al., 2021). The most rigorously studied example of indirect targeting comes from depression, where a number of studies have shown that cortical TMS targets that are more strongly connected to the subgenual cingulate cortex (sgACC) are associated with a greater antidepressant effect (Cash et al., 2019; Rosen et al., 2021; Weigand et al., 2018). However, some studies have demonstrated mixed data on the strength and direction of this association, suggesting that this relationship may not generalise to all cohorts or symptoms of major depressive disorder (Elbau et al., 2023; Gregory et al., 2025; Khosravani et al., 2025).

Beyond depression, Wang et al. (2014) identified a site in the left lateral parietal lobe with strong connectivity from the hippocampus, and showed that rTMS to this cortical target modulated the cortical-hippocampal network and enhanced associative memory. Similarly, Chen et al. (2022) mapped structural connectivity from the hippocampus to identify individualised superficial targets for TMS. Authors found that this was an effective method of modulating the hippocampal network, improving associative memory in individuals with mild cognitive impairment. In addition, Raij et al. (2018) identified a TMS target to modulate fear responses by localising a site in the ventrolateral prefrontal cortex functionally connected to the amygdala and ventromedial prefrontal cortex. Stimulating this cortical site with TMS was found to extinguish conditioned fear responses in a healthy population, and notably, TMS to a neighbouring region which was not connected to the deep target regions showed no effect (Raij et al., 2018). While these studies were not targeting findings from network mapping methods, their results demonstrate the principle of indirect targeting which could be applied to subcortical network mapping hubs. Researchers could consider pilot studies measuring engagement of the network prior to progressing to clinical trials (e.g., Kokkonen et al., 2024), employing study methods discussed above. Here, multiple potential targets could be compared for their ability to modulate the network, along with appropriate control sites or conditions. Further, the measurement of neurophysiological responses within clinical trials is also recommended to determine target/network engagement.

Selecting a target region considering feasibility and tolerability

Network mapping methods (and the mapping of connectivity from subcortical hubs) can localise more than one potential TMS target on the surface of the brain for the same clinical symptom. There are several factors that should be considered when deciding whether a site is viable for TMS, and whether the target can be optimised to give the best chance of clinical response. The first, related to the above section, is whether the region of the brain is easily accessible to stimulation from a TMS coil; whilst the identified region may be on the surface of the brain, the distance from the coil to the cortex differs across regions due to the anatomy of the brain and the head. For example, the distance from the scalp to the surface of the cerebellum is approximately three times greater than to the motor cortex (specifically the hand region) (Siebner et al., 2022). A larger coil-to-cortex distance leads to poorer focality and lower intensity of stimulation at the target site (i.e., depth-focality trade-off, discussed in the next section) (Hardwick et al., 2014; Siebner et al., 2022). In attempts to improve stimulation to deeper targets, a calculation was developed to adjust stimulation intensity to account for scalp-cortex distance (Stokes et al., 2005). However, it is unknown whether this calculation generalises to brain regions outside the motor cortex, or across different types of TMS machines and coils. Alternatively, several different methods have been proposed to account for distance between the coil and target region, including estimating the e-field within the target region of interest and adjusting stimulation intensity accordingly (Numssen et al., 2024). The e-field of a figure-of-eight coil has an approximate range of 0.9–3.4 cm (Deng et al., 2013), with 120% of resting motor threshold shown to penetrate an estimated 1.5 cm from the skull (Roth et al., 2007). However, when evaluating potential TMS target regions, it is still important to consider scalp-to-cortex distance, as these methods do not resolve issues of focality, and increasing stimulation intensity may also reduce tolerability.

Tolerability of TMS differs based on scalp location, as muscles and nerves are more densely populated in particular areas, such as frontal and inferior regions (around the face, neck and ear) which tend to cause more discomfort than medial/superior areas of the head (Fig. 2) (Meteyard & Holmes, 2018). Choosing a target in regions that cause discomfort may result in higher attrition rates in clinical trials and produce unwanted/unknown effects of pain (Han et al., 2019). Alternatively, it has become common in clinical trials and therapeutic practice to alter stimulation parameters to mitigate discomfort and reduce attrition (Borckardt et al., 2006; Fitzgerald & Daskalakis, 2013; Smith et al., 2021). The most commonly used methods include lowering stimulation intensity, titrating up to the optimal intensity across days or within sessions, or to alter the coil tilt or position to avoid muscles (Fitzgerald & Daskalakis, 2013). While these methods to enable stimulation to areas that cause discomfort (Smith et al., 2021), they may also result in suboptimal engagement of the neural structure being targeted (Baldi et al., 2024). Furthermore, targeting regions with stronger sensory input (e.g. pain, muscle twitches, auditory input) results in larger inadvertent neural activity due to co-stimulation of the sensory and salience systems which can lead to outcomes (e.g. EEG and fMRI signals) that are misattributed as stimulation effects (Biabani et al., 2024; Dowdle et al., 2018). These issues of tolerability may become increasingly relevant with accelerated TMS protocols on the rise, which deliver numerous sessions of TMS per day (Cole et al., 2020; Vaughn et al., 2024), and therefore may reduce the tolerability of TMS protocols that cause discomfort.

To evaluate the tolerability of potential target regions, a recently developed tool can be consulted to find ratings of pain, muscle twitch and annoyance at 43 sites across the scalp (Meteyard & Holmes, 2018)

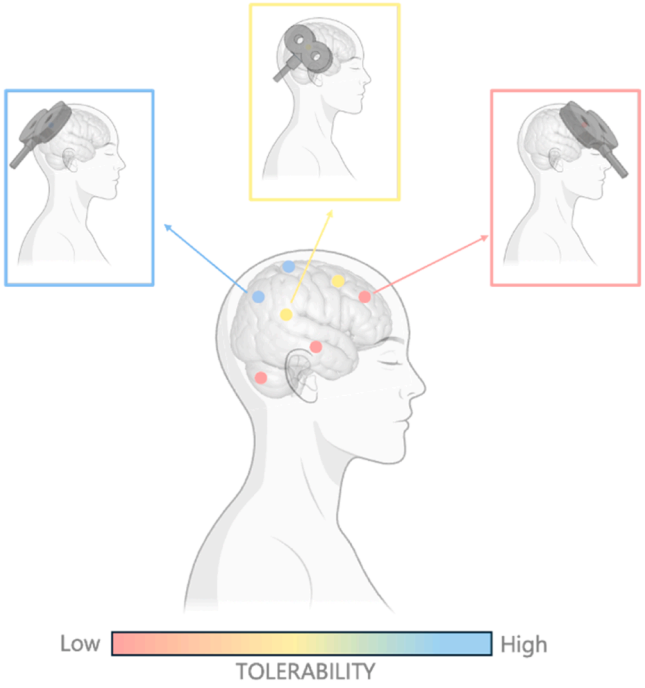

Fig. 2. Tolerability across Scalp Locations. Tolerability of stimulating potential target regions can be estimated using the TMS-SMART tool (https://tms-smart.info/). This tool indicates that frontal and inferior areas of the head (red) were associated with lower tolerance to TMS than medial/superior areas (yellow/blue). Figure created with BioRender. Younger, E. (2026) https://BioRender.com/zc4va80.

(https://tms-smart.info/). This resource can provide general (average) information across the scalp sites, or researchers can enter MNI coordinates and coil orientations to estimate the discomfort in the region closest to a proposed target. Note that these ratings are based upon a standard figure-of-eight TMS coil delivering single-pulses at a stimulation intensity of 50% maximum stimulator output, so may differ for repetitive protocols and different stimulation intensities. Researchers can use this tool to evaluate the tolerability of potential cortical targets localised by network mapping findings.

Defining a target considering the TMS induced electric field

Network mapping methods can localise hubs that vary in size and may be binary or continuous maps. These 'hubs' are determined by the analytical approach used in the original network mapping study. However, researchers will need to refine the specific region to target with TMS, and this may involve parameter choices such as thresholding, selecting a specific region of interest within the hub, and/or shifting the target location to ensure optimal stimulation of the intended neural structures. For example, Kokkonen et al. (2024) targeted the MNI coordinates at the centre of gravity of the cluster connected to all lesion locations causing cervical dystonia in Corp et al. (2019), and similarly, Taylor et al. (2026) targeted the peak MNI coordinates of the dysphoric and anxiosomatic symptom networks defined in Siddiqi et al. (2020). Yet one could also target a larger region of interest instead of specific MNI coordinates.

In each case, toolboxes such as SimNIBS (Thielscher et al., 2015; Fig. 3) can be helpful to model the e-field induced by the TMS coil placement and evaluate which areas are likely to undergo peak stimulation. This can be determined using a standard brain to define the target on a group level, or on an individual basis by importing a participant's structural MRI scan and simulating the e-field induced by different coil positions. The optimal coil position (or 'pose') can then be exported to neuronavigation software. This individualisation is especially important to consider in neurodegenerative populations where there is higher variability in coil to tissue distance and cortical folding patterns.

The intensity of the TMS e-field at a given target site is determined by several factors, including the site's distance from the coil and the anatomy of the underlying tissue (Numssen et al., 2023), and these should be taken into account when defining a target. Specifically, the e-field has an inherent depth-focality trade-off, whereby superficial regions are subject to stronger, more focal stimulation, while the induced e-field attenuates with greater distance from the coil (Numssen et al., 2023; Siebner et al., 2022). Therefore, it is likely preferable to define a target near the crown of the gyrus closer to the coil, where the induced current in the brain will be strongest and most focal, than in the sulcus where the induced e-field will be lower and less focal (Lynch et al., 2022) (modelled in Fig. 3B using SimNIBS software). There may be exceptions to this where reduced focality is acceptable, for example, in the case of a larger network hub spanning adjacent gyri, or to engage white-matter tracts identified through network mapping analyses using the structural connectome (Bowren et al., 2022; Horn et al., 2017). Different pulse types (e.g., biphasic pulses for repetitive TMS protocols) can also produce shifts in sites of neural activation given that TMS-evoked action potentials are dependent on current direction (Siebner et al., 2022). Similarly, the induced e-field is strongly influenced by the orientation of the TMS coil. Modelling work suggests that a primary target of a TMS pulse is axon terminals, and depolarisation is maximal when the TMS-induced current is parallel to these axons (Aberra et al., 2018; Siebner et al., 2022). Therefore, individualising the coil orientation to be perpendicular to the subject's gyrus in the brain region being targeted has been recommended (Gomez-Tames et al., 2018). Further discussion of coil orientation is provided in Supplementary file Section A.

If these factors are not considered, it is possible that the induced e-field will be higher in a neighbouring gyrus than in the target region (Numssen et al., 2023; Rajasekharan et al., 2025) (Fig. 3B). Regardless, there will be some stimulation of surrounding structures (Fig. 3C). Therefore, investigators may consider whether the adjacent gyri are also part of the target network, or whether inadvertent stimulation of this neighbouring region may have potentially unwanted effects, and in such a case, whether the target or coil angle/orientation could be modified to

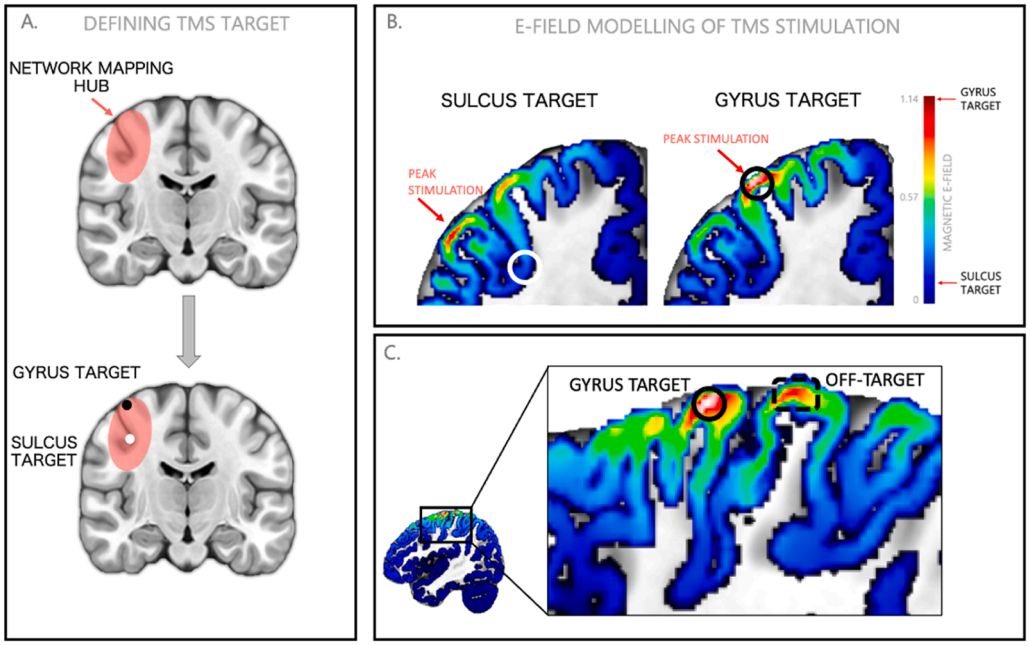

Fig. 3. E-field Modelling for Defining TMS Targets. (**A**) After identifying a cortical network hub, a specific target needs to be defined and optimised for TMS. Instead of defining the target deep in a sulcus, it may be beneficial to target the crown of the gyrus within the network hub. (**B**) E-field modelling shows that a target in the sulcus (left) will receive less intense stimulation and the peak e-field could instead hit a neighbouring gyrus. Alternatively, a target in the gyrus crown (right) is more likely to have stronger, more focal stimulation. (**C**) Researchers can consider if a high e-field may also be induced in a neighbouring gyrus, and whether this has the potential to inadvertently produce unwanted effects. In such a case, the target or coil angle/orientation could be modified to avoid or minimise this.

avoid this. For example, some studies have shown that TMS efficacy in depression is related to the target's magnitude of negative functional connectivity to the subgenual cingulate cortex, and that it may be preferable to avoid neighbouring structures with positive connectivity (Fox et al., 2012; Weigand et al., 2018). This could also be the case if the direction of functional connectivity identified in network mapping studies is different between neighbouring gyri. For example, in LNM, a lesion network map shows the brain regions that have synchronous (positive connectivity) and asynchronous activity (negative connectivity) with the lesion location, which is estimated using the spontaneous fluctuations in the blood oxygenated level-dependent signal across the brain at rest (Fox, 2018; Fox et al., 2005). It has been suggested that the direction of connectivity resulting from network mapping analyses may indicate whether TMS should be used to try to increase or decrease neural activity of target network to ameliorate symptoms (Corp et al., 2019; Fox et al., 2014; Joutsa et al., 2022; Siddiqi et al., 2024) (the type of TMS that might be most suitable to employ has been a matter of debate in network mapping studies, therefore, we expand on this discussion in Supplementary file Section B 'The type of TMS to use based on network mapping findings'). In summary, a range of factors, such as coil to target distance, tissue anatomy, and the orientation of the TMS coil, will influence the induced e-field in the target region. E-field models can be generated to help define and optimise the target for TMS and can be used in conjunction with neuronavigation software. If laboratories do not have access to this software, they could consider alternative approaches for scalp localisation of MNI-defined cortical targets (e.g. MNI2CPC probabilistic cortex-to-scalp mapping tool; https://transcranial-brain-atlas.org/MNI2CPC/; (Liu et al., 2023)), while still taking into account the aforementioned factors.

Summary and conclusions

TMS is a promising treatment option for neurological and psychiatric disorders, however, for many conditions, there is a lack of a priori, reproducible evidence about which targets in the brain are likely to respond to neuromodulation (Button et al., 2013; Darby et al., 2019; Fox, 2018; Poldrack et al., 2017). Network mapping methods may offer a solution, as studies have shown these methods can localise reproducible brain networks underlying symptoms and disorders (Ganos et al., 2022; Joutsa et al., 2018; Younger et al., 2023; Zouki et al., 2023). The present review has highlighted practical considerations for researchers wishing to translate network mapping findings into TMS studies, including the selection of a target based on the nature of network mapping results, the modulation of subcortical network hubs via TMS to strongly connected cortical regions, feasibility and tolerability of TMS to structures identified by network mapping, and defining targets based on the TMS e-field distribution. Overall, this paper encourages the integration of the fields of network mapping and TMS, and provides guidance on key factors to consider when translating network mapping to future TMS trials.

CRediT authorship contribution statement

Juho Joutsa: Writing – review & editing, Conceptualization. **Peter J. Fried:** Writing – review & editing. **Andreas Horn:** Writing – review & editing. **Vincenzo Di Lazzaro:** Writing – review & editing. **Nigel C. Rogasch:** Writing – review & editing. **Robin F.H. Cash:** Writing – review & editing. **Jordan Morrison-Ham:** Writing – review & editing. **Elizabeth G. Ellis:** Writing – review & editing. **Ellen F.P. Younger:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Daniel T. Corp:** Writing – review & editing, Supervision, Conceptualization.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Given his role as Deputy Editor (Approaches, Neuroimaging), Robin Cash had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. Given his role as Deputy Editor (Disciplines, Neurology), Vincenzo Di Lazzaro had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.transm.2026.100314.

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