The Effects of Transcranial Stimulation on Language Related Large Scale Brain Networks

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Summary

The potential of brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), for therapeutic purposes in neurologic and psychiatric diseases is currently intensively investigated. The current article provides a framework about the nature of long term effects of TMS and tDCS, as seen after therapeutic brain stimulation. Using auditory verbal hallucinations as a specific example of language network computation error, we demonstrate that brain stimulation changes language network activity, simultaneously with clinical improvements. Furthermore, we show that these stimulation effects are propagated from the directly stimulated region to structurally and functionally connected remote areas. Thus, we conclude hypothesizing that brain stimulation induces neuronal plasticity via disrupting pathological network connectivity. This principle of action needs to be further investigated in epilepsy: as a diagnostic tool for the detection of essential nods (hubs) within the epileptic large scale network in the workup for disconnective surgergy and as a potential therapeutical option for modifying non-invasively the pathological activity within the epileptic network.

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Key words: Connectivity, transcranial stimulation, large scale networks, language system, auditory hallucinations

Die Effekte von transkraniellen Stimulationsverfahren auf Sprachnetzwerke

Das therapeutische Potenzial von Hirnstimulationstechniken wie der transkraniellen Magnetstimulation (TMS) und der transkraniellen Gleichstromstimulation (tDCS) für psychiatrische und neurologische Erkrankungen wird aktuell intensiv untersucht. Der vorliegende Artikel stellt die Grundlagen der langandauernden Effekte von TMS und tDCS auf das Gehirn dar, wie sie im Rahmen von therapeutischen Anwendungen der Hirnstimulationen beschrieben wurden. Bei verbalen auditorischen Halluzinationen, als spezifisches Beispiel einer Verarbeitungsstörung im Sprachsystem, zeigen wir, dass TMS und tDCS Hirnaktivität im Sprachnetzwerk verändert und dies zu Verbesserungen der klinischen Symptome führt. Wir zeigen, dass sich die Stimulationseffekte vom eigentlichen Stimulationsort zu strukturell und funktionell verbundenen Hirnregionen ausbreiten. Eine zusammenfassende Hypothese besagt, dass Hirnstimulation neuronale Plastizität durch die Unterbrechung pathologischer Netzwerk-Konnektivität verursacht. Dieses Wirkprinzip soll für die Epilepsie weiter untersucht werden: Als diagnostisches Mittel, um Hauptknoten (Hubs) des epileptischen Netzwerkes zu detektieren, zum Beispiel im Rahmen der Planung diskonnektiver Operationen, und als potenzielle therpeutische Option im Sinne einer nicht-invasiven Therapie, die pathologische epileptische Hirnaktivität modifiziert.

Schlüsselwörter: Konnektivität, transkranielle Stimulation, „large scale"-Netzwerke, Sprachsystem, auditive Halluzinationen

Effets de la stimulation transcrânienne sur les réseaux cérébraux à grande échelle liés au langage

Le potentiel des techniques de stimulation cérébrale, telles que la stimulation magnétique transcrânienne (TMS) et la stimulation transcrânienne à courant direct (tDCS), dans le traitement des affections psychiatriques et neurologiques fait l'objet d'études approfondies. Le présent article expose les bases des ef-

fets à long terme de la TMS et de la tDCS sur le cerveau, tels qu'ils sont constatés dans le cadre des stimulations cérébrales thérapeutiques. Dans les hallucinations auditives verbales, exemple spécifique d'un trouble du traitement dans le système du langage, nous montrons que la stimulation du cerveau modifie l'activité cérébrale dans le réseau du langage tout en induisant une amélioration simultanée des symptômes cliniques. Nous montrons également que les effets de la stimulation se propagent de l'endroit d'origine aux régions cérébrales présentant une connexion structurelle et fonctionnelle. L'hypothèse émise pour résumer est que la stimulation cérébrale entraîne une plasticité provoquée par l'interruption de la connectivité pathologique du réseau. Ce principe d'action doit faire l'objet d'autres recherches en épilepsie : comme moyen diagnostique, pour détecter les nœuds essentiels (hubs) du réseau épileptique, par exemple dans le cadre de la planification d'interventions chirurgicales de déconnexion, et comme option thérapeutique potentielle pour modifier l'activité épileptique pathologique dans le cerveau de manière non invasive.

Mots clés : Connectivité, stimulation transcrânienne, réseaux « large scale », système de langage, hallucinations auditives

Introduction

The present article aims to provide a survey of the effects of non invasive brain stimulation techniques such as transcranial magnetic and direct current stimulation (TMS and tDCS) on the human brain with a special focus on the language system. We will show that transcranial stimulation not only influences the directly stimulated area but also structurally and functionally connected large scale brain networks.

The article starts giving a definition and introduction of brain networks and thereafter centers on language related brain networks. Subsequently, we will focus on aberrations and processing failures in language brain network using auditory verbal hallucinations (AVH) as one specific example of speech related network errors and will conclude describing their treatment with transcranial stimulation.

Brain networks and their structural and functional connectivity

Since more than a century, anatomical connections between different brain areas via long- and short-range white matter fiber tracts have been matter of research. It is a well-known fact that structure and function of the brain are closely intertwined in mammalian brain. Recent methodological advances in non-invasive brain imaging such as diffusion tensor and functional brain imaging in combination with novel statistical tools for network modeling have increased our understanding of these brain networks and their structural and functional basis. Spatially distant brain areas that are functionally and structurally connected are organized in networks that share and exchange information. One major goal of the brain's network architecture is to facilitate functional flexibility despite a relatively fixed structure [1]. Large scale brain networks are defined as widespread brain regions showing specific functional connections. The functional connections can be measured with e.g. BOLD fMRI signal fluctuations and are defined as synchronized brain activity or, simply put, co-activation of different brain areas. Most importantly, coordinated and orchestrated functional activity of different brain areas varies with cognitive functions. Furthermore, functional connectivity during cognitive activity has to be distinguished from functional connectivity without any cognitive task. Among the most influential concepts of the last 2 decades are the so-called resting state networks (RSN) [2, 3]. These RSN are defined by synchronized spontaneous oscillations between the cortical areas in the absence of any cognitive demands. Several specific RSN have been identified in a bulk of studies, e.g. an executive control network, a salience network, a sensorimotor network, an auditory network, a visual network, a speech related network and a default mode network (DMN) [2, 3]. As mentioned above, these networks can also be measured during task related activity. The DMN is a RSN that is highly active during rest and becomes deactivated during any goal-oriented activity [2]. It is therefore also called "task-negative network". The deactivation during goal oriented activity distinguishes the DMN from the above mentioned other RSN, which show increased activity during cognitive tasks. The cerebral structures involved in the DMN comprise the posterior cingulate cortex, the precuneus, the inferior parietal cortex, the medial prefrontal cortex and the medial temporal lobe [2 - 6]. DMN activity is reflecting processes like internal mentation, the generation of self-referential spontaneous thoughts and task-independent introspection. For an efficient interaction with the environment the translation between the self-referential resting state (default mode) und non-self-referential goal-directed processes is important [7].

Summing up, brain networks are spatially distant brain areas with functional and structural connections and the goal to integrate specific, especially cognitive, brain functions.

Brain networks of the language system

Language processing demands a functional interaction of an extended set of cortical regions to accomplish at least two major functions: language comprehension and language production [8]. Any incoming auditory

sensory information is collected via the primary auditory cortex (PAC; Brodmann area (BA) 41) located in the transverse temporal gyrus, also called Heschl's gyrus. Traditionally, major language related cortical areas include Broca's area, consisting of the pars opercularis (BA 44) and the pars triangularis (BA 45) located in the inferior frontal gyrus, and Wernicke's area (BA 22, 42), localized in the superior temporal gyrus, the middle temporal gyrus, the inferior parietal gyrus and the angular gyrus.

Here, we will describe the "dual stream model" of the functional organization of language processing as published by Hickok and Poeppel [9]. See **Figure 1 B** for a rough schematic overview. This model assumes two distinct computational networks to process incoming acoustic speech information:

First, early spectrotemporal analysis of the acoustic stimulus in the PAC, phonological processing is performed in the middle and posterior parts of the superior temporal sulcus. Consecutively, the system diverges in the two subsystems, the dorsal and the ventral stream. The dorsal stream involves structures of the frontal lobe (Broca's area) and the premotor cortex and relates acoustic speech signals to frontal lobe articulatory networks. It is responsible for phonological processing and word production (sound to action).

The ventral stream consists of the posterior middle and inferior portions of the temporal lobes (lexical interface, partly Wernicke's area), which links phonological and semantic information and a more anterior portion (combinatory network). Functionally, the ventral stream links acoustic speech signals with conceptual-semantic representations and is thus responsible for speech comprehension (sound to meaning).

One important functionally defined region in this language network is the area Spt (Sylvian parietotemporal), located in the Sylvian fissure at the parietotemporal boundary. It is considered to be a sensorimotor interface between the sensory and motor speech systems [9]. It is located strongly left dominant, and is activated equally by the perception and reproduction of aurally or visually presented words (**Figure 1**).

These language areas are heavily connected via white matter fiber tracts. The most prominent frontotemporal white matter bundles are the arcuate fascicle and the superior longitudinal fascicle connecting the superior temporal gyrus with the premotor cortex and the superior temporal gyrus with Broca (BA 44) via the dorsal pathway. Furthermore, on the ventral way, the extreme fiber capsule system connects the temporal cortex with Broca (BA 45) and finally, the uncinate fascicle connects the frontal operculum of Broca's area with the temporal gyrus and the superior temporal sulcus. Even though dorsal and ventral stream are computationally distinct, the core concept of the dual stream model recognizes a highly dynamic interaction of language areas, as the acoustic speech network must interface with a conceptual system and the motor/articulatory system to successfully accomplish language comprehension and production [9].

Most importantly, functional connectivity analysis using BOLD fMRI revealed significant functional connectivity between Broca's area in the inferior frontal gyrus and Wernicke's area in the temporal cortex [10]. Thus, the structurally related speech areas also show intensive functional connections.

Abberations of the language system

Hallucinations, found in various neuropsychiatric disorders, are sensory deceptions, commonly defined as conscious perceptions that occur in the absence of a corresponding adequate external sensory stimulus. Neurobiological data on AVH are mainly collected in schizophrenia patients, as here AVH found in above 70% of the patients and even count as a diagnostic symptom. Studies demonstrated that AVH are associated with increased neuronal activity in cerebral areas responsible for language production and perception [11]. These observations not only apply for schizophrenia patients, but have also been found in patients with partial epilepsy suffering from concomitant hallucinations, and thus are understood as being independent of the

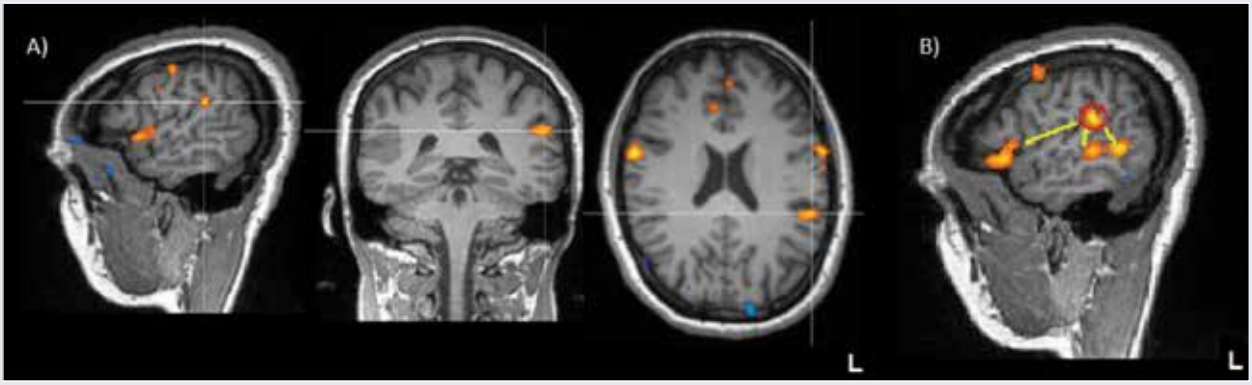

Figure 1: (A) Individual localisation of language areas during BOLD fMRI using a speech production task in a single subject. (B) Area Spt (red circle) serves as a sensomotoric language interface and is functionally connected (yellow arrows) to Broca's and Wernicke's area.

underlying disorder [12, 13]. Importantly, in AVH, activation of the PAC has been reported [11], interpreted as an integrative component of false perception that contributes to the physical quality of the hallucination and forming the subjective conviction that the perceived stimulus must come from any external side. Thus, PAC activation seems to be a constituting element of AVH generation, not only an epiphenomenon. Activation of Broca's and Wernicke's areas, or their contralateral homologs, during AVHs, have also been reported. Further, deep brain structures and the limbic system are involved with the cortical network, probably contributing to the affective and mnestic features of AVH in psychosis. Finally, the anterior insula and the anterior cingulate cortex show increased activity during AVH, both of them are critically involved in the discrimination of self versus external generated stimuli [14, 15]. Within the language network an increased functional connectivity between key players in the generation of AVH, namely the PAC, Wernicke's and Broca's area has been reported in resting state functional connectivity studies [16].

These functional alterations might be facilitated by structural changes in the brain fibers interconnecting the cortical language regions [17]. Thus, AVH might be caused by increased structural connections and pathologically increased activity within the language network.

Transcranial stimulation modifies brain networks

Whereas the effects of repetitive (r)TMS are due to depolarization of neurons and consecutive neuronal long-term depression or potentiation, tDCS modulates the neuronal membrane potential and consequently it's cortical excitability, potentially via shifts in Ca2+ and various neurotransmitters. High frequency TMS and anodal tDCS have excitatory effects, low frequency TMS and cathodal tDCS have inhibitory effects on cerebral cortex [18]. Importantly, short-term effects, occurring during or immediately after stimulation, and long-term effects, measurable hours and days after brain stimulation, have to be differentiated. In the following section, we will refer to long-term effects and, thus, the induction of neuroplasticity as observable when using brain stimulation techniques for therapeutic purposes.

Even though pharmacological treatment is the common therapeutic approach for AVH in schizophrenia, approximately 1/3 of the hallucinating patients are non-responders. In these patients, rTMS has been demonstrated as an effective therapy [19]. Recent studies have also demonstrated beneficial effects on AVH using tDCS [14, 20]. Pursuing a translation approach, the pathological increased brain activity in language related brain regions involved in the generation of AVH is targeted with brain stimulation techniques. Importantly, stimulation protocols with inhibitory effects are used to reduce and rebalance increased activity with the aim to normalize psychopathology, or in other words to diminish or extinguish the voices.

Brain activity can be measured by magnetic resonance (MR) arterial spin labeling (ASL), providing a quantitative measure of cerebral perfusion that is related to neuronal activity [21]. Compared with the estimation of cerebral blood flow (CBF) by positron emission tomography, no radiotracers have to be injected. ASL can, therefore, be applied in situations that require repeated examination and allows additional structural and functional MRIs to be measured within the same session. Robust changes to regional (r) CBF in motor and premotor areas have been demonstrated after rTMS to the motor cortex [18, 22]. However, a bulk of studies indicated that TMS not only affects the directly stimulated regions but also remote areas that are functionally and structurally connected [18, 23]. Furthermore, the ASL technique has successfully measured differences in rCBF between healthy individuals and schizophrenia patients [7] and more specifically, while psychopathological phenomena were present [24].

Hereafter, we describe an experiment where we investigated the effects of inhibitory rTMS [25] on cortical neuronal activity to treat AVH, using MR-ASL to measure rCBF before and after TMS [15]. Patients with pharmacoresistant AVH received a 10-day rTMS treatment to the left temporoparietal cortex. The stimulation location was individually defined using a language task during fMRI (**Figure 1**), which identified the sensorimotor language area Spt [9]. Navigation of the TMS coil was done with a neuronavigation system, targeting area Spt in each subject individually (**Figure 2**). Patients treated with rTMS showed positive clinical effects, which were indicated by a reduction in AVH scores [19]. rCBF significantly decreased in the PAC, Broca's area, Wernicke's area and the cingulate gyrus (**Figure 3**). Furthermore, the decrease in CBF in the PAC correlated with the decrease in AVH. Importantly, clinical response to rTMS therapy could be predicted by rCBF in the left superior temporal gyrus, identifying patients with the most impressive decrease of AVH after TMS, as having a significantly higher rCBF before TMS [26].

The main finding of the above mentioned study was a reduction of neuronal activity primarily within language related areas supporting AVH, as reflected by a CBF decrease after rTMS therapy, concurrently with a reduction of hallucinations. The CBF decreases are not explained by direct TMS effect, because they were remote from the directly stimulated temporoparietal area. Thus, our results strongly suggest a propagation of rTMS effects by functional and structural connections from the directly stimulated area Spt to Broca's area and the PAC.

As commented earlier in this article, area Spt serves as a sensorimotor interface between the frontally and temporally distributed language network. In fact, the data suggest that area Spt serves as a gateway into the hallucination-generating cerebral network that can be

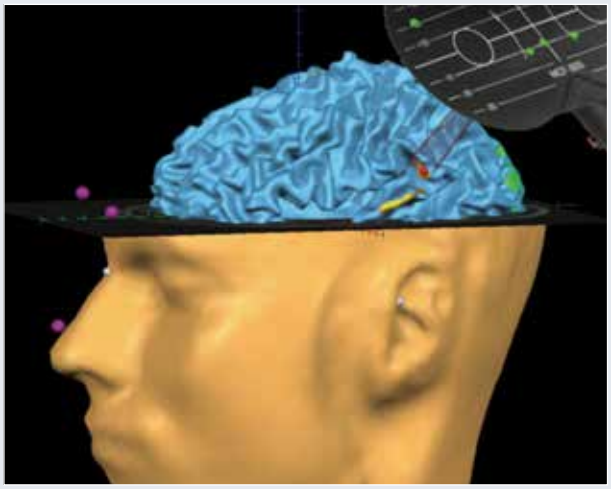

Figure 2: Neuronavigation to area Spt (red sphere) in a single subject. The individually defined language area Spt served as target point for rTMS in patients suffering from hallucinations.

modulated by rTMS. Moreover, the findings of the study further support the hypothesis of a key role of the PAC.

However, it remains possible that rTMS is inducing functional changes somewhere else in the "hallucination network" that itself produces a reduction in AVH and a secondary, downstream reduced activation of the PAC. In this framework, rTMS intervention would curtail signal propagation via the arcuate fasciculus between Broca's area, superior temporal gyrus and the PAC. Consequently, the disconnection, and not reduced PAC activity, would cause the improvement [15].

Next to TMS, also tDCS can be used to modulate the pathological brain activation seen during AVH and leading on the clinical level to improved psychopathology [14, 20]. In tDCS for AVH, the cathode is usually placed over the left temporal cortex and the anode over the left (or right) prefrontal cortex. Stimulation intensity varies from 1 - 2mA, applying daily sessions for about 10 days, 20min/day. A recent study investigated the effects of frontotemporal tDCS for the treatment of AVH on resting state connectivity, using seed based BOLD fMRI functional connectivity [14]. The authors reported altered functional connectivity between the brain regions of the language networks. Thus they found a reduction of AVH in combination with a reduction of resting state functional connectivity between the left temporoparietal junction with the left anterior insula and the right inferior frontal gyrus (Broca) but also increased connectivity between left temporoparietal junction with the left dorsolateral prefrontal cortex. Only the reduction of functional connectivity between left temporoparietal junction and the left anterior insula correlated to a reduction of AVH severity. Here again, this study clearly indicated that tDCS for the treatment of AVH induces modulations of resting state connectivity in brain networks, including speech and language networks and an accordance between the neurobiological and psychopathological findings

Discussion

The language system opens an interesting route to the understanding of the functional long-term effects of TMS and tDCS, as it is highly functionally specialized and intensively investigated in healthy populations and diseases states. Previous studies demonstrated that brain stimulation with TMS or tDCS does influence entire brain networks when used for therapeutic purposes, not only in AVH [14, 15] but also in aphasia, neglect and motor recovery after stroke [27]. In AVH, the studies showed that pathologically increased language network activity and/or connectivity are reduced, concurrently with symptomatic improvements. From a brain physiological and methodological point of view, study results strongly suggest a propagation of brain stimulation effects, spreading from the directly stimulated "gateway area" (here: area Spt) into the entire network (here: language network), most likely via structural and functional connections. Future studies will have to demonstrate, whether there is an optimal entry port into the network, yielding the best clinical results or whether the stimulation site is less important as effects are further disseminated into the network. Based on the available data, we hypothesize that brain stimulation is disrupting pathological brain network activity, thereby forcing the network to form alternative connections and finally producing neuroplastic changes. When using brain stimulation for the treatment of AVH, studies indicate that clinical improvements last for up to 3 months. We believe that at the end of this 3-month period the network steadily relapses, more and more employing former pathological brain circuits.

In a case series, we reported a pathological brain network in acoustic hallucinations of epileptic origin that matches the spatial distribution of the psychotic AHV network as reviewed here [12]. This observation strengthens the concept of clinically brain function being linked to specific anatomically defined networks. Pathological brain activity of different etiology and character would develop and propagate – at least in part – within these predefined networks.

Epilepsy has been conceptualized as a network disease, representing a system of nods and hubs involved in seizure generation, propagation, maintenance and termination [28]. With the emergence of new diagnostic tools in the clinical workup of epilepsies as quantitative EEG measures, electrical source imaging and simultaneous EEG/fMRI recordings, large scale epileptic networks are detected with a precision that allows to specifically target hubs by TMS in individual patients.

Recently, a protocol combining EEG with TMS, which aims at assessing both the diagnostic accuracy and the response to antiepileptic treatment in Genetic Generalized Epilepsy (GGE), resulted in an accuracy of 0.84 for the classification of healthy controls versus GGE and 0.76 for the classification of responder versus non-responder to antiepileptic medication [29]. Recent TMS

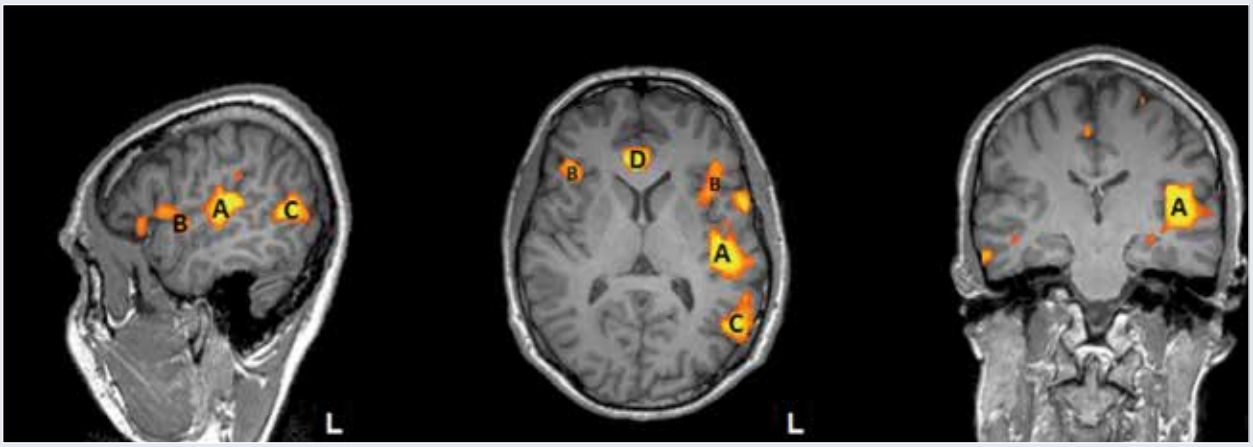

Figure 3: Cerebral blood perfusion (CBF) before vs. after 10 sessions of rTMS treatment of auditory verbal hallucination, group effects of 12 subjects, whole brain voxel wise analysis. CBF measured with MR-ASL, paired t-test, p < 0.05 (uncorrected), extended voxel treshold 250.
A significant decrease of CBF has been detected in [A] left the auditory cortex (x/y/z=-46/ -22/10), the [B] motor speech area bilaterally (Broca, x/y/z=38/26/8 and x/y/z=-39/22/5), the [C] left temporal cortex (Wernicke x/y/z=-54/-59/7) and [D] the anterior cingulate cortex (x/y/z=2/34/7).

work has shown that hyperexcitability of the motor cortex may predict resistance to pharmacological treatment in epileptic patients [30]. Currently, the therapeutic potential of transcranial magnetic stimulation techniques for the diagnostic issues and treatment of epilepsy is intensively investigated. A Pubmed search in January 2017 using the terms "transcranial stimulation" and "epilepsy" yields 645 published studies. However, the evidence for efficacy of rTMS for seizure reduction is still in discussion [31].

Conclusion

Summing up, studies suggest that transcranial stimulation techniques cause clinical improvements by interrupting pathological network activity via small electromagnetical impulses, thereby changing network connectivity and ultimately inducing neuronal plasticity in the entire network.

TMS is a technique that allows safely, noninvasively to probe virtually any cortical areas and by these entry gateways, modulate large-scale networks in physiology and pathology. Applied with simultaneous quantified EEG-measures and functional imaging technics TMS is promising as diagnostic tool to precisely detect network connectivity by inducing remote effects throughout the brain. Results may allow targeting of invasive diagnostic or treatment options in psychiatry as well as in epilepsy.

The results from rTMS in drug-resistant AHV in psychosis represent a translational approach having demonstrated a clinically benefit for the individual patient. In epilepsy the potential of rTMS as a non-invasive treatment of pathological epileptic network activity needs to and will be explored further in the future.

References

1. *Park HJ, Friston K. Structural and functional brain networks: from connections to cognition. Science 2013; 342: 1238411*
2. *Raichle ME, MacLeod AM, Snyder AZ et al. A default mode of brain function. Proc Natl Acad Sci U S A 2001; 98: 676-682*
3. *Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 2003; 100: 253-258*
4. *Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J Cogn Neurosci 2004; 16: 1484-1492*
5. *Jann K, Dierks T, Boesch C et al. BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. Neuroimage 2009; 45: 903-916*
6. *Jann K, Kottlow M, Dierks T et al. Topographic electrophysiological signatures of FMRI resting state networks. PLoS One 2010; 5: e12945*
7. *Kindler J, Jann K, Homan P et al. Static and dynamic characteristics of cerebral blood flow during the resting state in schizophrenia. Schizophr Bull 2015; 41: 163-170*
8. *Friederici AD. The brain basis of language processing: from structure to function. Physiol Rev 2011; 91: 1357-1392*
9. *Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007; 8: 393-402*
10. *Lohmann G, Hoehl S, Brauer J et al. Setting the frame: the human brain activates a basic low-frequency network for language processing. Cereb Cortex 2010; 20: 1286-1292*
11. *Dierks T, Linden DE, Jandl M et al. Activation of Heschl's gyrus during auditory hallucinations. Neuron 1999; 22: 615-621*
12. *Hauf M, Wiest R, Schindler K et al. Common mechanisms of auditory hallucinations-perfusion studies in epilepsy. Psychiatry Res 2013; 211: 268-270*
13. *Hubl D, Hauf M, van Swam C et al. Hearing dysphasic voices. Lancet 2007; 370: 538*
14. *Mondino M, Jardri R, Suaud-Chagny MF et al. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations*

and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. Schizophr Bull 2016; 42: 318-326

15. *Kindler J, Homan P, Jann K et al. Reduced neuronal activity in language-related regions after transcranial magnetic stimulation therapy for auditory verbal hallucinations. Biol Psychiatry 2013; 73: 518-524*
16. *Curcic-Blake B, Ford JM, Hubl D et al. Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. Prog Neurobiol 2017; 148: 1-20*
17. *Hubl D, Koenig T, Strik W et al. Pathways that make voices: white matter changes in auditory hallucinations. Arch Gen Psychiatry 2004; 61: 658-668*
18. *Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci 2007; 8: 559-567*
19. *Hoffman RE, Hawkins KA, Gueorguieva R et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Arch Gen Psychiatry 2003; 60: 49-56*
20. *Homan P, Kindler J, Federspiel A et al. Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. Am J Psychiatry 2011; 168: 853-854*
21. *Homan P, Kindler J, Hubl D, Dierks T. Auditory verbal hallucinations: imaging, analysis, and intervention. Eur Arch Psychiatry Clin Neurosci 2012; 262(Suppl 2): S91-95*
22. *Orosz A, Jann K, Wirth M et al. Theta burst TMS increases cerebral blood flow in the primary motor cortex during motor performance as assessed by arterial spin labeling (ASL). Neuroimage 2012; 61: 599-605*
23. *Hubl D, Nyffeler T, Wurtz P et al. Time course of blood oxygenation level-dependent signal response after theta burst transcranial magnetic stimulation of the frontal eye field. Neuroscience 2008; 151: 921-928*
24. *Homan P, Kindler J, Hauf M et al. Repeated measurements of cerebral blood flow in the left superior temporal gyrus reveal tonic hyperactivity in patients with auditory verbal hallucinations: a possible trait marker. Front Hum Neurosci 2013; 7: 304*
25. *Kindler J, Homan P, Flury R et al. Theta burst transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: results of a randomized controlled study. Psychiatry Res 2013; 209: 114-117*
26. *Homan P, Kindler J, Hauf M et al. Cerebral blood flow identifies responders to transcranial magnetic stimulation in auditory verbal hallucinations. Transl Psychiatry 2012; 2: e189*
27. *Kindler J, Schumacher R, Cazzoli D et al. Theta burst stimulation over the right Broca's homologue induces improvement of naming in aphasic patients. Stroke 2012; 43: 2175-2179*
28. *Zubler F, Gast H, Abela E et al. Detecting functional hubs of ictogenic networks. Brain Topogr 2015; 28: 305-317*
29. *Kimiskidis VK, Tsimpiris A, Ryvlin P et al. TMS combined with EEG in genetic generalized epilepsy: A phase II diagnostic accuracy study. Clin Neurophysiol 2016; pii: S 1388-2457(16)30669-1 Epub ahead of print*
30. *Badawy RA, Vogrin SJ, Lai A, Cook MJ. Does the region of epileptogenicity influence the pattern of change in cortical excitability? Clin Neurophysiol 2015; 126: 249-256*
31. *Chen R, Spencer DC, Weston J, Nolan SJ. Transcranial magnetic stimulation for the treatment of epilepsy. Cochrane Database Syst Rev 2016; 8: CD011025*

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