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Neurochemical Modulation in Posteromedial Default-mode Network Cortex Induced by Transcranial Magnetic Stimulation

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ABSTRACT

Background: The Default Mode Network (DMN) is severely compromised in several psychiatric and neurodegenerative disorders where plasticity alterations are observed. Glutamate and GABA are the major excitatory and inhibitory brain neurotransmitters respectively and are strongly related to plasticity responses and large-scale network expression.
Objective: To investigate whether regional Glx (Glutamate + Glutamine) and GABA could be modulated within the DMN after experimentally-controlled induction of plasticity and to study the effect of intrinsic connectivity over brain responses to stimulation.
Methods: We applied individually-guided neuronavigated Theta Burst Stimulation (TBS) to the left inferior parietal lobe (IPL) in-between two magnetic resonance spectroscopy (MRS) acquisitions to 36 young subjects. A resting-state fMRI sequence was also acquired before stimulation.
Results: After intermittent TBS, distal GABA increases in posteromedial DMN areas were observed. Instead, no significant changes were detected locally, in left IPL areas. Neurotransmitter modulation in posteromedial areas was related to baseline fMRI connectivity between this region and the TBS-targeted area.
Conclusions: The prediction of neurotransmitter modulation by connectivity highlights the relevance of connectivity patterns to understand brain responses to plasticity-inducing protocols. The ability to modulate GABA in a key core of the DMN by means of TBS may open new avenues to evaluate plasticity mechanisms in a key area for major neurodegenerative and psychiatric conditions.

Introduction

In the last two decades, resting-state fMRI (rs-fMRI) studies have identified the presence of certain components that fluctuate synchronously [1,2], which are thought to reflect the intrinsic functional architecture of the brain. One of the resting-state networks (RSN), the default-mode network (DMN), has been intensively investigated [3]. This network is comprised of posteromedial structures (precuneus/posterior cingulate cortex [PCC]), medial prefrontal cortex (mPFC), lateral inferior parietal lobes (IPL) and temporal nodes. The DMN shows high activity at rest, while its nodes exhibit decreased engagement during externally oriented tasks [4]. This network is compromised in several neuropsychiatric

Abbreviations: DMN, Default-mode network; GM, Grey Matter; IPL, Inferior parietal lobe; hr, High-resolution; MRS, Magnetic resonance spectroscopy; mPFC, Medial prefrontal cortex; mr, Medium-resolution; PCC, PosteriorCingulate/Precuneus; ROI, Region-of-interest; rs-fMRI, Resting-state functional magnetic resonance spectroscopy; RSN, Resting-state network; NIBS, Non-invasive brain stimulation; (i/c)TBS, (intermittent/continuous) Theta-burst stimulation; (r)TMS, (repetitive) Transcranial magnetic stimulation; tCr, Total Creatine; tNAA, Total N-Acetylaspartate; VOI, Voxel-of-interest; WM, White Matter.

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disorders, such as schizophrenia [5,6], autism [7], Alzheimer's disease [8,9], and even healthy aging [10]. Alterations in the DMN are often reflected by reductions in connectivity between nodes, reduced resting-state metabolism, and a lack of task-induced deactivation.

Glutamatergic and GABAergic neurons are the main excitatory and inhibitory constituents of the canonical microcircuit respectively [11], and hence mediate neuronal activity. Glutamate and GABA neurotransmitters can be non-invasively quantified in humans by MR spectroscopy (MRS) [12], and have consistently been associated with functional neuroimaging measures [13]. Specifically in the DMN, local GABA concentration has shown to predict task-induced deactivations [14], while glutamate showed an inverse pattern, and hence relates to reduced deactivations [15]. Intrinsic functional connectivity of the DMN is also mediated by GABA and glutamate [16]. Complementarily, MRS neurotransmitter measures in the DMN are sensitive to healthy and pathological aging [17,18].

In accordance with their fundamental role in mechanisms of neuroplasticity, GABA and glutamate imbalances [19,20] have been reported in the abovementioned conditions characterized by DMN dysfunction. For example, in Alzheimer's disease neuroplasticity is altered in association with a glutamate/GABA microcircuit dysfunction, which additionally shows complex interactions with Amyloid-beta deposition [21]. Therefore, the ability to modulate glutamate and GABA within the DMN after the application of plasticity-inducing procedures may offer a unique opportunity to evaluate the preservation of regional plasticity mechanisms in a key network for several diseases. Ultimately, brain plasticity responses in the DMN may also be useful to monitor disease progression or response to treatments.

The use of non-invasive brain stimulation techniques (NIBS), such as repetitive transcranial magnetic stimulation (rTMS), has emerged as an optimal methodological approach in humans to induce and evaluate plasticity mechanisms [22]. Patterned protocols of stimulation such as theta-burst stimulation (TBS) [23], can modulate cortical excitability producing long-term potentiation and long-term depression like phenomena, up to an hour after stimulation cessation. Physiological and pharmacological investigations revealed glutamatergic [24] and GABAergic [25] involvement in TBS-induced plasticity effects. Intermittent TBS (iTBS) tends to enhance cortical excitability, while continuous TBS (cTBS) usually produces inhibitory post-effects [23] both in the underlying stimulated tissue and in distal interconnected areas [26]. However NIBS after-effects are highly dependent on a variety of parameters [27] such as functional brain connectivity that mediates the neural and cognitive response to NIBS [26,28].

rTMS can directly modulate DMN expression [29,30] by targeting an accessible cortical node of this network; the left IPL. So far, it has been shown that stimulating this area modulates connectivity changes between DMN nodes [30,31] and enhances alpha rhythm [32]. In addition, MRS, that allows regional quantification of endogenous metabolites, represents a sensitive technique to capture NIBS after-effects [33–36] such as revealing increased GABA concentration in the motor cortex following cTBS [25]. These neurotransmitter modulations after stimulation have been shown to be functionally relevant, as GABA responsiveness to transcranial direct current stimulation was related to greater motor learning capacity and learning-related decrement of fMRI signal [37]. Furthermore other protocols able to elicit plasticity, such as learning paradigms, produce regional neurotransmitters modulations, essentially GABA changes, of similar magnitude to the ones produced by NIBS [38,39].

To the best of our knowledge, no study has so far addressed whether NIBS is capable to modulate GABA or glutamate measures within the DMN. The main objective of this investigation was to study whether a single TBS session would result in the modulation of neurotransmitter concentration in both local and distal DMN nodes (left IPL and PCC) assessed with MRS. Consequently, we applied individually-guided neuronavigated sham, intermittent or continuous TBS stimulation in-between two MRI acquisitions. A rs-fMRI sequence was also acquired before stimulation. We hypothesized that active rTMS would induce neurotransmitter changes, compared to sham stimulation in both local and distal areas. While this study is exploratory, we expected GABA increases after cTBS as in Stagg and colleagues [25] and a reversed effect after iTBS. We also hypothesized that the magnitude of neurotransmitter changes induced by rTMS in the distal node would be related to the intrinsic functional connectivity.

Methods

Participants

Thirty-six healthy right-handed young subjects (age = 23.50 [2.00]; 8 males), naive to stimulation, were randomly assigned to one of three experimental groups (Sham, iTBS or cTBS). Four subjects (1 male) were discarded from the MRS analysis, due to poor quality data. These subjects were not included in any analysis; data from 2 left IPL spectras were removed due to lipid contamination, and one PCC spectra was removed due to MRS acquisition problems. Final analyses included 30 subjects for the left IPL voxel (10 sham, 10 iTBS, 10 cTBS) and 31 subjects for the PCC spectroscopic voxel (11 sham, 10 iTBS, 10 cTBS). No differences regarding gender, age and education existed between groups (see SI for inferential tests and extended sociodemographic information). None of the participants had any neurological or psychiatric disorder or TMS contraindications [40]. All subjects gave informed consent and the protocol was in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Experimental design

The main experimental protocol consisted of a TMS session in-between two MRI acquisitions. In both MRI sessions, two MRS were acquired, one in the PCC and the other in the left IPL, along with a medium resolution (mr) structural acquisition (Fig. 1). Additionally, in the pre-stimulation session an rs-fMRI dataset was acquired. Prior to the main experimental day, subjects underwent an MRI acquisition that included a high resolution (hr)-3D structural and an rs-fMRI dataset, acquired for segmentation, co-registration and targeting purposes.

TMS

TBS was applied, according to previously described protocols [23], in-between two MRI sessions with a MagPro ×100 Stimulator (MagVenture A|S, Denmark) and an eight-figure coil (TBS and motor threshold protocols are fully described in SI). For the sham group, a sham coil was used mimicking the clicking sound. TMS position was held tangentially to the skull and rotated ≈30–50° from the midline thus being perpendicular to the dorsal part of the anterior occipital sulcus [41]. TBS was performed in a room adjacent to the MRI scanner and was neuronavigated with a stereotactic system (eXimia Navigated Brain Stimulation, Nexstim, Finland).

The stimulation target was individually defined as the coordinates within the left IPL that showed the highest correlation with other DMN nodes. We operationalized this concept in a similar way as described in the literature [29,31]. We created 7 mm spherical Regions-of-Interest (ROI)s in the mPFC (x,y,z = 0,51,−7),