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Transcranial Direct Current Stimulation Modulates Activation and Effective Connectivity During Spatial Navigation

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ABSTRACT

Background: Allocentric navigation declines with age and neurologic disease whereas egocentric navigation does not; differences that likely arise from maladaptive changes in brain regions mediating spatial (parietal cortex; hippocampus) but not procedural processing (caudate nucleus). Transcranial direct current stimulation (tDCS) holds promise for treating such decline given its ability to modulate neuronal excitability, but its effects have yet to be examined on spatial navigation.

Objectives/hypotheses: Using healthy young adults as a model, Study 1 intended to validate a novel spatial navigation paradigm using functional magnetic resonance imaging (fMRI). Using these data to determine targets for tDCS, Study 2 aimed to determine if 1) stimulation modulates activation in a polarity-specific manner; 2) stimulation results in global and/or task-specific activation changes; 3) activation changes are accompanied by changes in effective connectivity.

Methods: All participants underwent fMRI while learning allocentric and egocentric environments. Twelve participants completed Study 1. In Study 2, 16 participants were randomized to 20 min of tDCS (2 mA) using a montage with the anode over PZ and cathode over AF4 (P+F−) or the reverse montage (P−F+).

Results: Study 1 revealed that distinct networks preferentially mediate allocentric and egocentric navigation. Study 2 revealed polarity-dependent changes in activation and connectivity. The P+F− montage increased these measures in spatial regions, especially during allocentric navigation, and the caudate nucleus. Conversely, the P−F+ montage increased activation and connectivity in lateral prefrontal cortices and posterior hippocampus.

Conclusions: These findings support the neuromodulatory effects of tDCS in non-motor areas and demonstrate proof-of-principle for ameliorating age- and disease-related decline in navigational abilities.

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Learning and remembering how to travel from one location to another is critical in everyday life and involves the interaction between the allocentric and egocentric navigation systems. During allocentric navigation, individuals use spatial information about an external reference system (e.g., landmarks) to create a cognitive map of the environment and determine their position within it. This navigational approach relies on medial temporal lobe (e.g., hippocampus, parahippocampal gyrus) [1–5] and posterior/medial parietal regions [3], which is consistent with roles these regions play in spatial and associative processing. Additionally, Jerde and Curtis [6] recently presented evidence that the frontal eye fields (i.e., meeting point of the superior precentral sulcus and superior frontal sulcus) and intraparietal sulcus were critical for cognitive map formation and use. Conversely, egocentric navigation is based on an internal reference system and relies on a series of stimulus–response relationships that are highly specific and inflexible. This reliance on "habit" memory is most commonly associated with the striatum (caudate nucleus, putamen) [4].

While distinct, these cognitive approaches (and their corresponding brain regions) frequently interact. For example, the egocentric system is primarily engaged when traveling the same, overlearned route to work each day; however, a detour along this standard route would require allocentric processing wherein a

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cognitive map of the environment is accessed and a new route is planned. Allocentric navigation is known to decline with age [3,7,8] (also see review [2]) and to become impaired in a number of neurological populations, including those with mild cognitive impairment and Alzheimer's disease (see Refs. [9,10]). Thus, identifying methods of enhancing allocentric navigation may ultimately result in functional improvement in such populations. The current report establishes proof-of-principle for the use of non-invasive brain stimulation in this regard.

Transcranial direct current stimulation (tDCS) has been shown to modulate cognitive functioning in a manner consistent with stimulation polarity (e.g., see Ref. [11] for a review). A recent study demonstrated that tDCS effectively modulates more basic aspects of allocentric and egocentric processing [12]. Similarly, low frequency repetitive transcranial magnetic stimulation (rTMS) to the parietal cortex has been shown to disrupt spatial processing [13]. Several studies have paired tDCS and functional magnetic resonance imaging (fMRI) to investigate its effects on various motor [14] and cognitive systems [15]. While such studies have validated the physiological effects of tDCS, they have generally relied on data acquired during the resting-state. Navigation is an active process so the neurophysiological effects of stimulation may be most accurately assessed via task-based fMRI.

The current two-part report is the first, to our knowledge, to combine tDCS and fMRI in the assessment of spatial navigation. In Study 1, we used fMRI to validate a novel spatial navigation paradigm. As discussed below, the results of this study revealed functionally related yet highly distinct neural networks mediating allocentric and egocentric navigation. In Study 2, we used these results to determine anodal and cathodal electrode placements and randomized participants to 20 min of tDCS using either a "parietal enhancing" montage with the anode over site PZ and the cathode over AF4, or the reverse "prefrontal enhancing" montage. Participants underwent fMRI immediately after stimulation and the results yield encouraging evidence for the utility of tDCS in enhancing activation within, and effective connectivity between, brain regions involved in allocentric navigation. We enrolled healthy young individuals in both studies in order to (1) validate our paradigm and approach and (2) establish the "normal" effects of stimulation without age- or disease-related confounds.

Study 1

As discussed above, the allocentric and egocentric systems are known to interact and this is presumably facilitated by shared brain regions/networks. Thus, our first goal was to identify these shared regions. Despite any potential overlap, we predicted that allocentric processing would preferentially engage brain regions that mediate spatial and relational/associative processing (e.g., parietal regions, parahippocampal cortex, hippocampus) to a greater extent than egocentric processing. Conversely, we expected that egocentric processing would engage brain regions involved in "habit" or procedural knowledge, such as the caudate nucleus. Therefore, our second goal was to examine difference in activation during allocentric and egocentric navigation.

Methods

Participants

A total of 13 healthy, right-handed adults completed a brief neuropsychological protocol to ensure they were cognitively intact (see Table 1). One participant could not tolerate the fMRI environment and was excluded from the study. Thus, data from 12 participants (7 male) were included in Study 1. Exclusion criteria included a history of (1) neurological disease or injury (e.g., epilepsy, stroke, moderate – severe traumatic brain injury) (2) mental illness (e.g., depression, bipolar disorder, schizophrenia), (3) sensory (especially visual) impairments that limit the ability to take part in the study (4) learning or attentional disorder; (5) history of (or current) alcohol or drug abuse/dependence; (6) any MRI contraindication as defined by the American College of Radiology. The Emory University Institutional Review Board and the Atlanta VAMC R&D Committee approved the study and all participants provided informed written consent.

Table 1
Demographics and neuropsychological performances of the participants from Study 1. Standard deviations shown in parentheses.

Age (years)	25.8 (4.0)
Education (years)	16.8 (2.7)
RBANS (Standard scores)	103.7 (6.0)
Immediate memory	106.8 (14.2)
Visuospatial/constructional	100.8 (11.3)
Language	101.3 (11.8)
Attention	105.7 (7.2)
Delayed memory total score	105.0 (10.5)
Trail Making Test (T-scores)	
Part A	49.7 (12.8)
Part B	54.1 (8.0)
Beck Depression Inventory II (raw scores)	3.1 (3.4)
Beck Anxiety Inventory (raw scores)	3.1 (2.6)

Stimuli

We created a total of eight 3-dimensional environments using MazeSuite 2.0 (www.mazesuite.com), which is a publicly-available program designed specifically for navigational neuroimaging research [16]. There were four allocentric (apartment, movie theater complex, city-scape; English garden) and four egocentric environments (forest, supermarket, office, desert). Two environments (allocentric = English garden; egocentric = desert) served as practice stimuli in both Studies 1 and 2. The remaining 6 environments were used during fMRI scanning (described below). Although virtual environments have been used to examine spatial navigation in previous fMRI research [3,17–19], several factors may have confounded those studies. First, previous research used tasks in which the participant could use one or both navigational approaches and also typically did not instruct participants on how to perform the task (i.e., allocentric vs. egocentric processing). Therefore, we developed environments that were specifically designed to engage either allocentric or egocentric navigation (Fig. 1). To reinforce the particular approach, we provided explicit instructions on how participants should attempt to remember each environment. For the allocentric environments, participants were instructed to create a cognitive map using the spatial relationship between the landmarks (or key features) within the environment and to ignore the sequence of turns. For the egocentric environments, participants were instructed to remember the sequence of left vs. right turns and were told that forming a cognitive map would be useless since each of these environments used the same map.

A second limitation of previous research is that participants have been able to freely explore the environment; which could result in different processing strategies and exposure times, especially in those who are less familiar with virtual navigation. Therefore, we created videos that standardized the path through each environment; thereby ensuring comparable exposure across participants. These 60" videos were assembled into four runs that were 8'6" in duration (324 volumes) and consisted of six – 60" active blocks (one video comprised the entire block) that alternated