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Modulating phonemic fluency performance in healthy subjects with transcranial magnetic stimulation over the left or right lateral frontal cortex

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ABSTRACT

A growing body of evidence have suggested that non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), can improve the performance of aphasic patients in language tasks. For example, application of inhibitory rTMS or tDCs over the right frontal lobe of dysphasic patients resulted in improved naming abilities. Several studies have also reported that in healthy controls (HC) tDCS application over the left prefrontal cortex (PFC) improve performance in naming and semantic fluency tasks. The aim of this study was to investigate in HC, for the first time, the effects of inhibitory repetitive TMS (rTMS) over left and right lateral frontal cortex (BA 47) on two phonemic fluency tasks (FAS or FPL). 44 right-handed HCs were administered rTMS or sham over the left or right lateral frontal cortex in two separate testing sessions, with a 24 h interval, followed by the two phonemic fluency tasks. To account for possible practice effects, an additional 22 HCs were tested on only the phonemic fluency task across two sessions with no stimulation. We found that rTMS-inhibition over the left lateral frontal cortex significantly worsened phonemic fluency performance when compared to sham. In contrast, rTMS-inhibition over the right lateral frontal cortex significantly improved phonemic fluency performance when compared to sham. These results were not accounted for practice effects. We speculated that rTMS over the right lateral frontal cortex may induce plastic neural changes to the left lateral frontal cortex by suppressing interhemispheric inhibitory interactions. This resulted in an increased excitability (disinhibition) of the contralateral unstimulated left lateral frontal cortex, consequently enhancing phonemic fluency performance. Conversely, application of rTMS over the left lateral frontal cortex may induce a temporary, virtual lesion, with effects similar to those reported in left frontal patients.

1. Introduction

Verbal fluency tasks require the generation of words either starting with a given letter (e.g. S) in phonemic fluency tasks, or words belonging to a category (e.g. animals) in semantic fluency tasks, within a given time frame. Verbal fluency tasks are thought to require language processes such as lexical retrieval and semantic memory (e.g. Henry and Crawford, 2004; Koerts et al., 2013; Shao et al., 2014; Vonberg et al., 2014; Whiteside et al., 2016). They are also thought to require executive processes such as the voluntary generation of non-overlearned responses and the ability to inhibit inappropriate responses (i.e. words not fitting the criteria) (e.g. Milner, 1975; Stuss and Alexander, 1998; Lezak, 1983, 2004). Executive functions refer to a variety of general purpose control mechanisms thought to modulate and organize more basic cognitive sub-processes to achieve effective behaviour (Stuss and Levine, 2002). The prefrontal cortex (PFC) is widely acknowledged to make a fundamental contribution to executive functions.

Lesion studies have suggested that the functional organization of the PFC may be lateralized (Stuss and Alexander, 2007; Shallice and Gillingham, 2012). A key example of this is that executive functions linked to verbal fluency have been associated with left PFC, since the seminal report of Milner (1964). It has been repeatedly reported that performance on verbal fluency tasks is impaired following lesions in the left frontal cortex (e.g. Baldo and Shimamura, 1998; Miceli et al., 1981; Newcombe, 1969; Pendleton et al., 1982; Vilkki and Holst, 1994), especially for phonemic fluency tasks (Benton, 1968; Milner, 1964; Perret, 1974; Stuss et al., 1998). For example, Baldo and Shimamura (1998) reported that patients with left prefrontal lesions generated

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fewer items than controls on verbal fluency tasks. Robinson et al. (2012) documented that phonemic fluency impairments were sensitive and specific to left lateral frontal lesions, in particular left inferior frontal gyrus lesions. The authors also documented that performance on semantic fluency task was sensitive but not specific to frontal lobe lesions. In line with this, Baldo et al. (2006) reported two patients with aphasia who exhibited a double dissociation between phonemic and semantic fluency performance. The authors suggested that the left frontal cortex is critical for phonemic fluency while the left temporal cortex is critical for semantic fluency. A recent study have investigated the anatomical correlates of phonemic and semantic fluency using voxel-based and region-of-interest-based lesion-symptom mapping in 93 patients with ischemic stroke. The results suggested that phonemic and semantic fluency overlap in the left inferior frontal gyrus and insula. However, semantic fluency involved also left medial temporal regions (Biesbroek et al., 2016).

Neuroimaging studies have also indicated that verbal fluency tasks induce extensive activation of the frontal lobe, with a focus on the prefrontal cortex and dorsolateral prefrontal cortex (e.g. Herrmann et al., 2006; Kubota et al., 2005; Ehlis et al., 2007; Nishimura et al., 2015; Ravnkilde et al., 2002; Sanjuan et al., 2010; Tupak et al., 2012). Both left and right inferior frontal cortices have been shown to activate when healthy right-handed subjects perform phonological tasks (Chee et al., 1999; Devlin et al., 2003; Shibahara, 2004; Tremblay et al., 2004). However, Wagner et al. (2014), in a functional MRI meta-analysis of brain activation during verbal fluency tasks in HC reported that the most prominent clusters were in the left inferior/middle frontal gyrus (LIFG/LMFG) and the anterior cingulate gyrus. For phonemic fluency, the meta-analysis of the coordinates revealed one cluster covering the LIFG/LMFG (BA 6, 9, 44, 45, 47) the left insula (BA 13) and an additional cluster involving left and right anterior cingulate gyrus (BA 24, 32).

Interestingly, a study using tractography showed that abnormalities of the frontal aslant tract (FAT) were correlated with measurements of phonemic fluency but not semantic processing or naming in patients with primary progressive aphasia (Catani et al., 2013). The FAT connects the inferior frontal gyrus (pars opercularis) to the anterior cingulate cortex and medial regions of the superior frontal gyrus such as pre-supplementary motor and anterior cingulate areas. These findings suggest that phonemic fluency depends on tract projecting to adjacent regions of the inferior frontal gyrus (Catani et al., 2013).

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been shown to improve the performance of aphasic patients in language tasks (e.g. Martin et al., 2009; Naeser et al., 2005; Baker et al., 2010; Fiori et al., 2011; Flöel et al., 2011; Fridriksson et al., 2011; Monti et al., 2008, 2012; Marangolo et al., 2013). Non-invasive brain stimulation studies have also reported an improvement in naming abilities following application of inhibitory rTMS or tDCs over the right frontal lobe of dysphasic patients (e.g. Naeser et al., 2004; Martin et al., 2004; Kang et al., 2011). This finding has often been linked to the increased right hemisphere activation reported in aphasic patients by functional imaging studies (e.g. Naeser et al., 2004). These studies have documented an "over-activation" of the right hemisphere (RH) language homologues in aphasic patients (Belin et al., 1996; Martin et al., 2005; Naeser et al., 2004; Perani et al., 2003; Rosen et al., 2000). It has been argued that this over-activation of the RH is related to transcallosal disinhibition leading only to partial or incomplete recovery. Such increased RH activation would represent maladaptive plasticity and lead to a dead-end, inefficient strategy for recovery (Lefaucheur, 2006; Belin et al., 1996; Naeser et al., 2004, 2005; Rosen et al., 2000; Price and Crinion, 2005). rTMS and tDCS stimulation over the right frontal lobe of aphasic patients are thought to reduce this maladaptive right hemisphere over-activation.

Several brain stimulation studies have also investigated in HC the effects of tDCS application over the left PFC in HC in naming and sentence generation tasks. For example, Fertonani documented that anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) significantly improve naming in HC (Fertonani et al., 2010). Cerruti and Schlaug (2009) applied tDCS over the left and right DLPFC. The authors found that anodal but not cathodal stimulation of left DLPF improved performance and on the remote associates test (RAT), a complex verbal task requiring participants to generate a word that forms a compound noun or a two-word phrase with each of three given cue words.

Brain stimulation studies have also reported that stimulation over the left inferior frontal gyrus enhanced verbal fluency in healthy young adults. For instance, Iyer et al. (2005) found improved phonemic fluency after anodal left inferior frontal gyrus stimulation. Meinzer et al. (2012) showed that in an fMRI scanner HC produced significantly more words in a semantic fluency task during real anodal tDCS than sham, while the fMRI demonstrated tDCS increasing functional connectivity in the language network. Penolazzi et al. (2013) reported that anodal tDCS over the left inferior frontal gyrus increased semantic fluency in HC after an interval of approximately 18 min. Vannorsdall et al. (2012) reported increased semantic fluency, but no effect on phonemic fluency, in HC after anodal stimulation of the left dorsolateral prefrontal cortex. Cattaneo et al. (2011) reported that anodal tDCS over LIGF significantly improved the performance of HC on phonemic and semantic fluency tasks. In contrast, Vannorsdall et al. (2016) using a paradigm similar to Cattaneo et al. (2011) failed to report anodal tDCS effects on verbal fluency (see also Cattaneo et al., 2016 for a response and Price 's et al., 2015 meta-analysis concluding that anodal tDCS over left frontal regions has reliable effects on language functions).

The studies reported so far for verbal fluency in HC have mainly contrasted the effects of tDCS with sham, rather than with other frontal areas. The sample of HC used tended to be rather small (e.g. n = 10 participants in the Cattaneo et al., 2011 study) raising the possibility that particular individuals may have inflated some of the reported effects. No consideration has been given to the potential effects of practice effects despite the fact that they have been previously documented on phonemic fluency tasks (e.g. Bird et al., 2004). Recently, Cattaneo et al. (2016) reported practice effects over two sessions on verbal fluency tasks if the same cues were used across both sessions but not if alternate versions of the tasks were used across sessions. Moreover, despite the known improvement in language tasks following application of TMS and/or tDCS over the right hemisphere or right frontal lobe, to the best of our knowledge, so far, no study has investigated the effects of TMS and/or tDCS over the right PFC on phonemic fluency tasks.

The aim of our paper was to investigate in a large sample of HC the effects of inhibitory rTMS over left and right lateral frontal cortex on phonemic fluency tasks and to evaluate the potential contribution of practice effects. We decided not to investigate semantic fluency tasks since previous work of one of us suggested that performance on semantic fluency tasks is not specific to frontal lobe damage (Robinson et al., 2012) and may involve temporal regions (e.g. Biesbroek et al., 2016).

2. Experimental investigation

2.1. Materials and methods

2.1.1. Participants

Healthy controls (HC) were assigned to two independent groups: *experimental* and *control*. The participants in the *experimental group* were administered rTMS, sham and the cognitive baseline and phonemic fluency tasks. The participants in the *control group* were administered only the phonemic fluency tasks.

Both the *experimental* and the *control* groups were recruited from the students' population of University of Palermo. All participants were native Italian speakers. In the experimental group there were 44 right-handed participants (6 males, 38 females) with a mean age of 23.9 (Standard Deviation 3). In the control group there were 22 right-handed