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Modulation of frontal effective connectivity during speech

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ABSTRACT

Noninvasive neurostimulation methods such as transcranial direct current stimulation (tDCS) can elicit long-lasting, polarity-dependent changes in neocortical excitability. In a previous concurrent tDCS-fMRI study of overt picture naming, we reported significant behavioural and regionally specific neural facilitation effects in left inferior frontal cortex (IFC) with anodal tDCS applied to left frontal cortex (Holland et al., 2011). Although distributed connectivity effects of anodal tDCS have been modelled at rest, the mechanism by which 'on-line' tDCS may modulate neuronal connectivity during a task-state remains unclear. Here, we used Dynamic Causal Modelling (DCM) to determine: (i) how neural connectivity within the frontal speech network is modulated during anodal tDCS; and, (ii) how individual variability in behavioural response to anodal tDCS relates to changes in effective connectivity strength. Results showed that compared to sham, anodal tDCS elicited stronger feedback from inferior frontal sulcus (IFS) to ventral premotor (VPM) accompanied by weaker self-connections within VPM, consistent with processes of neuronal adaptation. During anodal tDCS individual variability in the feedforward connection strength from IFS to VPM positively correlated with the degree of facilitation in naming behaviour. These results provide an essential step towards understanding the mechanism of 'online' tDCS paired with a cognitive task. They also identify left IFS as a 'top-down' hub and driver for speech change.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method, which can be used to modulate spontaneous cortical activity in the human brain in a polarity-dependent way (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001). Increasingly, the method is used as a therapeutic tool (Hummel et al., 2005; Boggio et al., 2008; Baker et al., 2010). Recent functional neuroimaging studies have investigated how changes in connectivity within resting-state networks are related to stimulation. For example, anodal tDCS, thought to increase cortical excitability, has been shown to alter connectivity within large-scale functional networks when delivered either before (Keeser et al., 2011; Pena-Gomez et al., 2011; Polania et al., 2011; Pereira et al., 2012; Polania et al., 2012) or during resting-state functional magnetic resonance imaging (fMRI) (Meinzer et al., 2012). However, the mechanism by which an externally applied field may interact and modulate neuronal activity during a given cognitive task-state and how it relates to changes in behaviour has yet to be determined. The present study is unique in this regard. Here, we used Dynamic Causal Modelling (DCM) to explore changes in effective connectivity during a concurrent tDCS-fMRI study of overt picture naming. Resulting model parameters from the DCM were used to provide a measure of both the strength and direction of neuronal interactions between pre-specified left frontal regions known to be important for speech production (Penny et al., 2004; Penny et al., 2010; Friston, 2011). Using this approach our data provide novel insights into the underlying neuronal dynamics of anodal tDCS that operate on the naming network.

In some cognitive and neurobiological models, cognitive functions are specified in distributed, inter-connected, overlapping and highly parallel processing networks (Hebb, 1949; Horwitz, 2003). This theoretical framework has been used to characterize a variety of different complex cognitive skills, including picture naming (Seidenberg and McClelland, 1989; McClelland and Rogers, 2003). From this perspective, connections within a distributed naming network can be altered and differentiated via exposure, or experience-based learning. Similarly, behavioural and neural facilitation, or priming, of naming performance can also be seen as mediated via refinement and adjustment of connections between collaborating brain regions (Buchel et al., 1999; Weiller and Rijntjes, 1999).

The neural correlate associated with learning and facilitation is neural priming, which is characterized by a decrease in focal brain activity reflecting processes of neuronal adaptation (Henson, 2003; Grill-Spector et al., 2006). Neuronal adaptation is mediated by changes

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in effective connectivity between and within regions of the neural network (Buchel et al., 1999; Weiller and Rijntjes, 1999; Pleger et al., 2006). Consistent with predictions of neuronal adaptation, we previously demonstrated that anodal tDCS applied to the left inferior frontal cortex during overt picture naming concurrent with fMRI had a regionally specific neural priming effect on the BOLD signal in left inferior frontal sulcus (IFS) and left ventral premotor cortex (VPM). Priming of the neural response (decrease in BOLD signal) significantly correlated with the behavioural priming of naming response times (Holland et al., 2011). This response profile suggests that anodal tDCS promotes neural efficiency during naming.

How these neural adaptation effects are mediated by changes in effective connectivity remains unclear. Considering these data in the context of a learning framework, one may predict that facilitatory tDCS effects would be mediated by changes in inter-regional connectivity affected by anodal tDCS (Weiller and Rijntjes, 1999), or in intra-regional activity via self-connections (Penny et al., 2004). To explicitly test these predictions in the present study we used DCM to determine: (i) changes in the strength and direction of neuronal coupling within and between left IFS and VPM during anodal tDCS compared to sham; and, (ii) how, at an individual level, the variability in effective connectivity values between these same two frontal regions related to variations in observed facilitation of picture naming behaviour (faster naming response times – RTs) during anodal tDCS.

Materials and methods

Participants

10 right-handed, healthy native speakers of English (7 females, mean age 69 years; range 62–74 years old) participated in a functional neuroimaging study of overt picture naming concurrent with anodal tDCS. All participants had normal hearing and no previous history of metallic implants, neurological or psychiatric disease. All participants were left hemisphere dominant for speech production as determined by a previous fMRI naming study. The simple main effect of anodal tDCS on the naming network in the same subjects has been reported previously (Holland et al., 2011).

Experimental design

We targeted left frontal activity using 2 mA anodal tDCS or sham stimulation delivered for 20 min during an fMRI study of overt spoken picture naming. To avoid problems of tDCS and sham group comparability with regard to common confounding variables (e.g., age and sex) we used a within subject cross-over design where each of our 10 subjects served as his/her own control. In our previous study (Holland et al., 2011) we investigated both order and cross-modal repetition effects as each picture was presented twice across two fMRI blocks on each scanning day: once with the target's spoken name as a cue and once with an acoustic control cue (a noise-vocoded speech cue). For the DCM analysis, we were only interested in the simple main effect of anodal tDCS vs. sham during naming compared to rest. We therefore included data only from the first scanning block on each scanning day and collapsed across auditory cue types. This ensured that we avoided any potential confounds of – and interactions with – the expected behavioural and neural priming effects of practice (order) or cross-modal repetition (cues) which would be associated with repeated exposure of items to be named on each scanning day. See Fig. 1 for a visualization of the study and task design. Full details of stimuli used and experimental procedures have been reported previously (Holland et al., 2011).

On their first scanning day, during their first naming block half the participants (N = 5) received sham stimulation. On their second scanning day, the order of intervention was reversed i.e., they received an A-tDCS naming block first. The remaining five participants had the opposite order of intervention across scanning days. Using this sequencing, the order of intervention was fully counterbalanced across participants and scanning days. A minimum of 5 and maximum of 7 days separated the two scanning days. This approach permitted measurement of both the behavioural and neural consequences of anodal tDCS during: (i) real anodal tDCS, and (ii) sham stimulation. Fig. 1A displays the run procedure.

The order of stimuli was pseudo-randomized. In their first scanning day, during their first naming block, participants saw each of the 107 high frequency monosyllabic pictures to name paired with either a word or noise cue. Participants then saw the same 107 pictures paired with the remaining cue type in the second scanning day's first

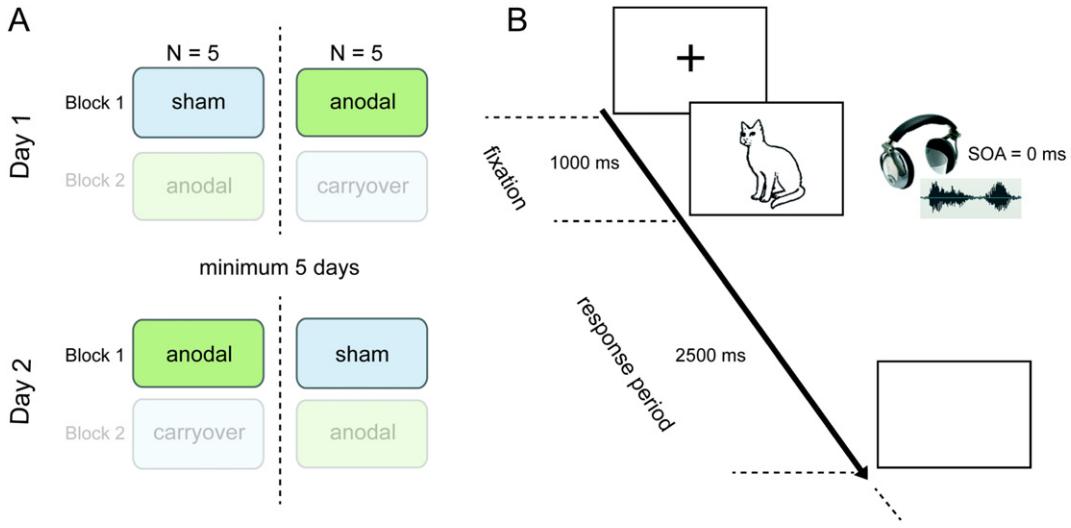

Fig. 1. Experimental procedure. (A) Timeline of the Experimental Run Procedure. This graphically displays the two, counterbalanced orders of intervention used. Block 1 and Block 2 refer to the tDCS run order within a scanning day. For the DCM analysis, only data only from the first scanning block on each scanning day was included. (B) Timeline of the Experimental Event Procedure. A typical sequence involving presentation of a fixation cross, a picture to be named and an auditory cue in the concurrent fMRI and tDCS (anodal or sham) naming task. After a 1000 ms fixation cross pictures were displayed simultaneously with the presentation of an auditory cue (SOA = 0 ms) which was either a spoken word that matches the picture/cat/or noise control item i.e., same word spectrally rotated and noise vocoded. Each picture remained on screen for 2500 ms and participants were instructed to name aloud the object as quickly and as accurately as possible. Brain images were continuously acquired, tDCS was continuously delivered and speech responses were audio-recorded.