Hemispheric Dominance for Task Dependent Frontal Lobe Function & Its Relationship to Language Lateralization and Handedness

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Abstract

The present study investigates a potential method to optimize effective functional localization strategies for both language regions and the dorsolateral prefrontal cortex (dlPFC) while in a scanner. This functional task combines elements of creative problem solving, executive decision making based on an internal rule set, and working memory. Retrospective analysis was performed on a total of 58 unique participants (40% female, $M_{\text{age}} = 42.84$ years, $SD_{\text{age}} = 16.51$). Of these participants, 47 were classified as right-handed, 7 were classified as left-handed, and 4 were classified as “mixed-handed” or ambidextrous according to the Edinburgh Handedness Inventory. The imaging data was judged by two blinded investigators to assess language and dlPFC dominance while using the motor cortex activation to confirm that participants engaged in the task. We show that 25% of right handed individuals seem to have a dominant dlPFC localized to the right hemisphere rather than the assumed left, and more than a quarter of left handers were dominant in their left hemisphere. Given the clinical relevance of dlPFC dominance, this task appears to be an evidence-based technique for determining appropriate dlPFC target for the purposes of neuromodulation (e.g. TMS).

Introduction

Handedness is considered to be one of the more obvious functional asymmetries within the human brain. The neural representation of handedness can be visually confirmed using neuroimaging. Less obvious functional asymmetries, such as language, creative problem-solving, and executive decision making require further investigation to determine neurological lateralization. Language regions (e.g., Wernicke’s and Broca’s areas) as well as the dorsolateral prefrontal cortex (dlPFC) constitute key functional targets for various therapeutic interventions (Avissar, 2017). The dlPFC is predominantly associated with frontal-executive skills, such as working memory, decision-making, creativity, and motor planning, and is functionally and reciprocally related to deeper prefrontal areas involved in mood regulation (Miller, 2001). Hemispheric localization varies to some degree with handedness, however, no heuristic used to correlate handedness with language or dominant dlPFC provides certainty. For instance, among a majority of right-handed individuals, dominant language function is most often localized to the left hemisphere. For many left-handed individuals, language may be lateralized to the left hemisphere as well; however, in contrast to right-handers, many left-handed participants will actually show either right hemisphere or bilateral representation.

Effective localization is highly important for decreasing the functional risks associated with neurosurgery and may be useful for determining placement for effective non-invasive stimulation techniques (e.g., transcranial magnetic stimulation, TMS). Repetitive TMS (rTMS) has been shown to mitigate subgenual cingulate hyperactivity in patients with refractory depression, nearly toward levels of healthy patients (Hadas, 2019). However, most literature on the use of rTMS for patients with depression report rTMS application over the left dlPFC rather than the right, assuming that right-handers have a dominant dlPFC on the left hemisphere (George, et al., 2010; George, 2013; Eche, 2012; Perera, 2016). Importantly, it is not

uncommon for patients to have a negative reaction to right dlPFC rTMS, yielding agitation or mania, requiring switching to the contralateral dlPFC to provide the desired therapeutic effects.

Early imaging experience suggested that depressed patients appear to have decreased activation of the dlPFC with inverse increased activation of the subgenual prefrontal region. Both neurosurgical navigation and rTMS targeting protocols have occasionally deployed seed analysis to determine stimulation sites or establish the bounds of a surgical field. For instance, one technique for localizing the dlPFC involves an anticorrelation seed analysis of the subgenual cingulate (Biver, 1994; Baxter Jr, 1989; Galyner II, 1998; Mayberg, 2005; Chen, 2013; Liston, 2014; Fox, 2012). These techniques have been used to attempt to improve treatment outcomes. In this vein, the present study attempted to use a method to optimize effective functional localization strategies for both language regions and the dlPFC using an fMRI task that combines elements of creative problem solving, executive decision making based on an internal rule set, and working memory.

Methods

Retrospective analysis was performed on a total of 58 unique participants (23 females, $M_{\text{age}} = 42.84$ years, $SD_{\text{age}} = 16.51$). Of these participants, 47 were classified as right-handed, 7 were classified as left-handed, and 4 were classified as “mixed-handed” or ambidextrous according to the Edinburgh Handedness Inventory.

MRI acquisition was performed on a 1.5 T Siemens Espree scanner equipped with a 16-channel head coil (Erlangen, Germany). A structural image was acquired for the purposes of co-registration with functional data. The T1 weighted anatomical sequence was magnetization-prepared, rapid-acquisition gradient-echo (MPRAGE) ($TR = 1810\text{ms}$; $TE = 3.50\text{ms}$; $\text{FoV} = 180 \times 240\text{mm}$; resolution 1mm isotropic). Each participant obtained blood-oxygen level dependent (BOLD) imaging at rest and with task-dependent activation. Resting state bold images were 8 minutes and 20 seconds long. This functional sequence was acquired with a TR of 2500 ms, $TE = 30$ ms, $\text{FoV} = 192 \times 192$ mm, resolution 4 mm isotropic and 200 spatial volumes. The task based BOLD acquisition was similar except fewer volumes— a total of 140 bringing the scan to 5 minutes and 50 seconds. The active task performed during the BOLD sequence was designed to engage the dorsolateral prefrontal cortex (dlPFC) through patient decision-making and creativity. Participants were trained by a technician prior to entering the scanner. While in the scanner, patients were presented with a series of slides containing 3 words; for each slide, patients were instructed to choose one of the words and perform a hand movement that creatively represented the chosen word (Figure 1, Appendix A). This active task was a block-based paradigm, constituting 25 seconds of rest (looking at a cross on the screen), followed by 25 seconds of the described activity.

This task takes advantage of many dlPFC functions including working memory and internally generated decision making. The movement corresponding to the words the patient chose elicits the hand and thumb region of the motor cortex and encourages working memory, as well as internal rule making. Working memory was also highlighted when patients were required to choose a word that had not

previously been demonstrated. Because these functions have been linked to the dlPFC, the combination of these actions elicited the desired functional network.

Efforts were made to minimize excess motion and to encourage an alert and relaxed state throughout the exam. Data was analyzed using workstations equipped with the Invivo Dynasuite program and other statistical software programs and compared with independent components analysis seed-based correlation analysis, and a power spectral transformation. Computer scoring and human cross checking was performed to ensure adequate processing of artifacts, proper co-registration and appropriate selection of relevant data for final interpretation.

A board-certified neurologist and board certified neuropsychologist verified language and dlPFC localization. Neurology and radiology peer review was performed on completed data sets for quality assurance and for interpretation consensus. Engagement in the task was judged based on whether or not there was significant BOLD activation in the motor strip, primarily in the hand knob area. The imaging data was judged by these two blinded investigators for dominant language hemisphere and dominant dorsolateral prefrontal cortex (dlPFC). Inter-rater reliability was defined by agreement with the 'official' judgment and evaluated by joint probability of agreement.

Results

All 58 patients' fMRI scans were evaluated by two investigators who were blinded to the handedness of the individual for dominant language hemisphere and dominant dorsolateral prefrontal cortex (dlPFC). Dorsolateral prefrontal cortex agreement between the two investigators who were blinded to the handedness of the individual was 90.6% (58 scans out of 64 scans), and language dominance agreement between the investigators was 93.8% (60 scans out of 64). Agreement on the correct activation pattern for which hand was utilized for the task was 100% (47 right handed patients, 7 left handed patients, and 4 ambidextrous patients). Of the 47 right handed patients, 35 (74%) were left hemisphere dominant for dorsolateral prefrontal cortex and 12 patients (26%) were right hemisphere dominant for dorsolateral prefrontal cortex. Of the 7 left handed patients, 5 (71%) were right hemisphere dominant for dlPFC, and 2 (29%) were left hemisphere dominant. Of the ambidextrous patients, 3 (75%) were right hemisphere dominant, and 1 (25%) was left hemisphere dominant. Of the 54 right and left handed individuals, 40 (74%) showed opposite hemisphere dominance for dlPFC and 14 (26%) participants showed same hemisphere dominance for dlPFC. 7 (13%) participants, of the 54 right and left handed participants, showed same hemisphere dominance for language and 47 (87%) participants showed opposite dominance for language. Of the 4 participants who were ambidextrous, 3 (75%) showed opposite hemisphere dominance for dlPFC and 1 (25%) participants showed same hemisphere dominance for dlPFC. Moreover, 2 (50%) participants, of the 4 ambidextrous participants, showed same hemisphere dominance for language and 2 (50%) participants showed opposite dominance for language.

All 58 patients received repetitive transcranial magnetic stimulation, with 54% (31 patients) reporting a clinically significant change in their Beck Depression Inventory scores (30% decrease in scores). Among

these 58 patients, one of them received treatment at a different TMS center and was stimulated on the hemisphere opposite the dominant dlPFC. This patient was right handed, and appeared to have a dominant dlPFC localized in the right hemisphere. The initial TMS center they were treated at stimulated the assumed left hemisphere; consequently, the patient reported feeling worse both verbally and on several intake forms (e.g., Beck Depression Inventory, Beck Anxiety Inventory, and Patient Depression Questionnaire). After reviewing the patient's scans and determining where the dominant dlPFC might be located, we stimulated the right dlPFC. The patient subsequently reported a decrease in Beck Depression Inventory and Beck Anxiety Inventory scores by 65.22% and 30.77%, respectively.

Discussion

Using the fMRI scans, two blinded investigators assessed language and dlPFC hemispheric dominant. We found a 90.6% agreement on dominant dorsolateral prefrontal cortex, and a 93.8% agreement on language localization. In this retrospective analysis, we show that 25% of right handed individuals seem to have a dominant dlPFC localized to the right hemisphere rather than the assumed left, and more than a quarter of left handers were dominant in their left hemisphere. Of the 54 right and left handed individuals, 74% showed opposite hemisphere dominance for dlPFC and 26% participants showed same hemisphere dominance for dlPFC. 13% of participants showed same hemisphere dominance for language and 87% participants showed opposite dominance for language. Of the 4 participants who were ambidextrous, 75% showed opposite hemisphere dominance for dlPFC and 25% participants showed same hemisphere dominance for dlPFC. 50% participants, of the 4 ambidextrous participants, showed same hemisphere dominance for language and 50% participants showed opposite dominance for language. The task completed in the scanner seems to be an efficient way to localize a potential dlPFC target for purposes of TMS.

The patient who received treatment opposite their dominant dlPFC hemisphere reported feeling worse both verbally and on several intake forms (e.g., Beck Depression Inventory, Beck Anxiety Inventory, and Patient Depression Questionnaire). After reviewing the patient's scans and determining where the dominant dlPFC might be located, we stimulated the right dlPFC. The patient subsequently reported a decrease in Beck Depression Inventory and Beck Anxiety Inventory scores by 65.22% and 30.77%, respectively.

Limitations of this current study include the small number of participants, and the small number of left handed participants compared to right handed participants. Using self-reported intake measures such as the Beck Depression Inventory is another limitation, as they are subject to biases in honesty and introspective ability, and interpretation of questions.

Based on the current study, it appears possible that effective localization of the dominant dlPFC is important for improving the efficacy of therapeutic stimulation techniques, such as rTMS, and for decreasing functional risks associated with neurosurgery. While the number of participants is small, over half of the 58 patients who received rTMS treatments reported a clinically significant change in the Beck

Depression Inventory scores. Tasks similar to the method used with functional imaging may be one way for effective TMS targeting, as it allows for the patient to activate a region that encapsulates creative problem solving, executive decision making, and working memory.

Another interesting question that could be subject for future research is where the dominant dlPFC would be localized for individuals who were forced to become right handers. This could potentially be why some right handed individuals had a dominant dlPFC localized in their right hemisphere rather than their left. Further research regarding effective targeting is required to determine the most efficient way to localize brain regions responsible for creativity, problem solving, and decision making based on an internal rule set.

Declarations

Ethical Approval

All procedures were in accordance with the Declaration of Helsinki, reviewed and approved by the Institutional Review Board prior to enrollment and all participants provided written informed consent.

Consent to Participate

Patients have consented to participating in this fMRI imaging study

Consent to Publish

Patients have given consent for publication

Authors Contributions

Name	Location	Role	Contribution
Barshen Habelhah, M.A.	Neurological Associates – The Interventional Group	Corresponding author	Data collection and analysis, site management, drafting of the manuscript
Kennedy Mahdavi, B.S.	Neurological Associates – The Interventional Group	Author	Data collection and analysis, revision of the manuscript
Margaret Zielinski, B.S.	Neurological Associates – The Interventional Group	Author	Data collection and analysis
Sergio Becerra, B.S.	Synaptec Network	Author	Data analysis, revision of the manuscript
Alexander Bysritsky, M.D.	University of California, Los Angeles	Author	Revision of the manuscript
Michael Mamoun, M.D.	CNS Health	Author	Contribution of participants
Taylor Kuhn, Ph.D.	University of California, Los Angeles	Author	Data analysis, statistical analysis, revision of the manuscript
Sheldon Jordan, M.D.	University of California, Los Angeles	Principle investigator, Author	Study design and conceptualization; revision of manuscript

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Competing Interests

The authors report no conflicts of interest

Availability of Data and Materials

Data will be made available to qualified users upon formal request

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Figures

Frog
Wave
Crab

+

Figure 1

Active Task “On” Slide. Active Task “Off” Slide.