

The Compensatory Role of the Frontal Cortex in Mild Cognitive Impairment: Identifying the Target for Neuromodulation

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Abstract

Introduction: Development of individualized neuromodulation techniques for mild cognitive impairment (MCI) is a feasible practical goal. Preliminary research exploring the brain-level compensatory reserves on the base of neuroimaging is necessary. **Methods:** Twenty-one older adults, representing a continuum from healthy norm to MCI, underwent functional MRI while performing two executive tasks—a modified Stroop task and selective counting. A functional activation and connectivity analysis were conducted with the inclusion of a BRIEF–MoCA covariate. This variable represented the difference between the real-life performance measured by Behavior Rating Inventory of Executive Function (BRIEF) and the level of cognitive deficit measured by Montreal Cognitive Assessment (MoCA) Scale, an ability to compensate for impairment. **Results:** Both tasks were associated with activation of areas within the frontoparietal control network, along with the supplementary motor area (SMA) and the pre-SMA, the lateral premotor cortex, and the cerebellum. A widespread increase in the connectivity of the pre-SMA was observed during the tasks. The BRIEF–MoCA value correlated, first, with connectivity of the left dorsolateral prefrontal cortex (LDLPFC) and, second, with enrollment of the occipital cortex during the counting task. **Conclusion:** The developed neuroimaging technique allows identification of the functionally salient target within the LDLPFC in patients with MCI.

Keywords: mild cognitive impairment; executive functions; fMRI; functional connectivity

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Introduction

Neurocognitive disorders are a major burden of the aging population (Hugo & Ganguli, 2014). While dementia is a frequent cause of death, even mild cognitive impairment (MCI) is associated with increased mortality (Bae et al., 2018). The incidence of MCI is high: 6.7% for ages 60–64, 8.4% for 65–69, with a subsequent increase up to 25.2% for ages 80–84. Neurocognitive disorders dramatically affect quality of life (Hugo & Ganguli, 2014), and a key contributor to maladaptation is executive dysfunction (Marshall et al., 2011).

Treatment options for MCI are limited. Cholinesterase inhibitors, commonly used to treat dementia, along with other drugs showed no benefit in MCI (Petersen et al., 2018). Thus, the development of nonpharmacological approaches for the improvement of cognitive functioning in MCI is feasible. The clinical application of neurophysiological research has resulted in an increased use of neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). While there is currently insufficient evidence to

evaluate the efficacy of these methods in MCI, some trials show promising results (Drumond Marra et al., 2015).

In a study by Drumond Marra et al. (2015), 34 patients with MCI were randomized for 10 sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex (LDLPFC) or sham TMS. The intervention resulted in enhanced everyday performance according to the Rivermead Behavioural Memory Test, with the effect lasting at least one month (Drumond Marra et al., 2015). According to another study, rTMS of the LDLPFC in MCI leads to compensatory recruitment of the frontoparietal control network (FPCN), which may explain its beneficial effects (Solé-Padullés et al., 2006). Artificial stimulation during neuromodulation has similarities with the natural functional adaptation of the brain observed in cognitive decline—increased recruitment of the cortex during challenging tasks, especially in the frontal areas (Clément, Gauthier, & Belleville, 2013; Naumczyk et al., 2017). This mechanism is also in line with the gold standard of neuropsychological rehabilitation: since memory training is proven to be ineffective, promoting compensations that improve everyday life is the main aim of rehabilitation (Wilson, Gracey, Evans & Bateman, 2009). At the same time, the importance of adjustment of the neuromodulation protocol on the base of neuroimaging is discussed, since MCI is a heterogenous phenomenon (Anderkova, Eliasova, Marecek, Janousova, & Rektorova, 2015). Along with evaluation of the clinical efficacy of neuromodulation, it is important to continue improving these techniques.

In the current study, we evaluate the organization of executive functions in MCI in conjunction with everyday functioning. As an a priori hypothesis, we assume that the top-down regulatory influences of the frontal cortex during an artificial task reflect the same brain-level mechanisms that allow compensation for cognitive decline in real life. We aim to reveal these mechanisms using functional connectivity analysis. This study is forming a basis for the development of individualized neurostimulation approaches.

Methods

Participants

Participants were selected among older adults (45 years and older) who volunteered to participate in the project. First, a structured interview and a neurological examination were performed to exclude participants with neurological and psychiatric diseases other than MCI. Second, a neuroimaging

inclusion criterion was applied; that is, a structural brain MRI scan graded as 0 or 1 on the Fazekas scale (absent or minor white matter lesions; Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). Any other brain damage, including any findings with a Fazekas rating of 2 or higher, served as an exclusion criterion, in order to avoid excessive heterogeneity of the sample. The study included 21 adults aged 45–71 years (median 57; 1st quartile 52; 3rd quartile 59.5), representing a continuum from healthy norm to MCI. Subjects with lower cognitive levels did not enter the study, because of their failure to fit into the Fazekas 0–1 range. We did not aim to define a clear margin between normal aging and MCI within the scope of the study, as this is problematic in this borderline group.

All participants underwent a cognitive assessment, performed by the same trained examiner, that included the Montreal Cognitive Assessment Scale (MoCA; Nasreddine et al., 2005), the Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000), the Luria Memory Words Test (Luria, 1980), and the Trail Making Test (Delis, Kaplan, & Kramer, 2001). Executive functioning in daily life was self-rated using the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). To account for emotional factors, the Hospital Anxiety and Depression Scale (HADS) was also included into the assessment (Zigmond & Snaith, 1983).

The protocol and informed consent form were approved by the Ethics Committee and the Institutional Review Board of the Research Center of Neurology, and all participants signed the informed consent form before entering the study.

fMRI acquisition and preprocessing. MRI was performed with a Siemens MAGNETOM Verio 3T scanner (Erlangen, Germany) located at the Research Center of Neurology. Functional images were acquired using T2*-gradient echo imaging sequences (TR 3000 ms, TE 30 ms, FA 90, voxel size 3x3x3 mm³, FOV 192 mm). Four extra functional volumes were acquired at the start of the session and discarded by the scanner software in order to prevent the usage of artifactual data obtained before the magnetic equilibrium is reached. A three-dimensional structural image consisted of a sagittal T1-weighted 3D-MPRAGE sequence (TR 1900 ms, TE 2.5 ms, FA 9, voxel size 1x1x1 mm³, FOV 250 mm).

All participants underwent two fMRI sessions with a block design with an interval of no less than 48 hours:

a simplified version of a classical Stroop task (Stroop; Stroop, 1935) and an original selective counting paradigm developed at our center (Count). Each task consisted of four active and four rest blocks with a duration of 30 s (4 min total). During the Stroop session, the rest periods (fixation cross) alternated with a slideshow consisting of 20 stimuli (1.5 s each): a word indicating a color (red, blue, green, or yellow) was presented on the display, written in either congruent or conflicting font color. The participants were required to inwardly answer “yes” if the color of the word corresponded to the text. During the Count task, eyes-open rest periods alternated with the selective counting task: the participants were instructed to inwardly count up from one, omitting the numbers divisible by three (one, two, four, five, seven, etc.). Before both sessions, a 5- to 10-min training was performed outside the scanner. Such simplified variants of executive tasks specifically address the population of cognitively impaired patients and allow further transfer of the technology to patients with dementia.

Data were analyzed in MATLAB 2017b (<http://www.mathworks.com>), with the use of the statistical parametric mapping software SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) and CONN17f (<http://www.nitrc.org/projects/conn>). A standard preprocessing protocol was utilized and included motion correction, slice-timing correction, realignment, co-registration of functional and anatomical data, normalization into the Montreal Neurological Institute (MNI) stereotactic space, segmentation of the average structural image into tissue images (grey matter, white matter, and CSF volumes) and smoothing with an 8-mm Gaussian kernel. All coordinates are presented in MNI space (x, y, z).

To evaluate block consistency, the raw activation data were extracted with the use of the MarsBaR toolbox (<http://marsbar.sourceforge.net>), and a comparison between blocks was performed with the SPSS v22 (<http://www.ibm.com/products/spss-statistics>) package using a general linear model.

The functional neuroimaging results were rendered and visualized with the use of the MRICroGL program (<http://www.cabiatl.com/mricrogl>).

Functional activation and connectivity analysis. Statistical parametric maps for each participant were calculated using a general linear model. To compute group activation maps, a second-level analysis was

performed using one-sample T-tests with $p < .001$ uncorrected at the voxel level.

The task-related functional connectivity analysis aimed to evaluate the regulatory influences of the areas within the frontal lobes during the executive tasks. On the basis of the activation analysis for both the Stroop and Count conditions, we identified the key areas within the frontal cortex, and the regions of interest (ROIs) for the connectivity analysis were constructed as spheres of 10-mm radius around the centers of these clusters (see Results section, Table 2).

Based on the assumption that the task-based connectivity of the frontal areas might correlate with the ability to compensate for cognitive decline in real life, we included the second-level covariates BRIEF and BRIEF–MoCA into the analysis. To compute the BRIEF–MoCA value, we transformed absolute BRIEF and MoCA scores into scales from 0 to 10 (MoCA: 0 for the lower and 10 for the higher value in the sample, BRIEF: 0 for the higher and 10 for the lower value in the sample) and then calculated the difference between these ratings. A higher BRIEF–MoCA value represents better executive functioning in everyday life, despite a cognitive deficit.

Denosing of the functional data included linear regression of the confounding effects of the white matter, CSF, correction for realignment and scrubbing, and the application of a band-pass filter of 0.008–0.09 Hz. Functional connectivity evaluation was performed using Pearson’s correlation analysis with a subsequent Fischer transformation during the first-level analysis. Multiple-comparison adjustments were implemented with a false discovery error rate (FDR) of $q < .05$ at the cluster-level, given a voxel-wise statistical threshold of $p < .001$ uncorrected. A Bonferroni correction was applied for the number of ROIs entered into the ROI-to-voxel connectivity analysis.

Results

Cognitive assessment data. The results of the cognitive assessment are summarized in Table 1. According to the MoCA scale (Nasreddine et al., 2005), the study sample included a continuum from healthy norm to MCI, with a range of 25–30. The evaluation of executive functions with the FAB revealed no significant impairment (score 17–18 of 18), while the results of the more sensitive TMT indicated some decline in performance. According to the BRIEF, the participants experienced variable

difficulties with self-regulation in daily life. While these tests gave us only a general impression regarding the level of executive functioning, this battery, in combination with the neuroimaging procedure, was already very demanding for our sample of older adults.

HADS ratings indicated that the majority of the subjects did not have clinically significant anxiety or depression, and it is thus unlikely that emotional factors had any valuable influence on cognitive performance.

Table 1
The results of the cognitive assessment.

	Median	Min	First Quartile	Third Quartile	Max
Montreal Cognitive Assessment Scale (MoCA)	28	25	25	29	30
Frontal Assessment Battery (FAB)	18	17	17	18	18
Behavior Rating Inventory of Executive Function (BRIEF)	123	88	107	139	156
Luria Memory Words Test (quantity of words memorized after 5 trials, of 10)	9	7	9	10	10
Luria Memory Words Test (quantity of words recalled after 30-min interference, of 10)	8	2	7	9	10
Trail Making Test, part A (time in seconds)	34	21	28.5	42.5	65
Trail Making Test, part A (normalized percentile)	30	10	10	60	80
Trail Making Test, part B (time in seconds)	89	54	59.5	103.5	154
Trail Making Test, part B (normalized percentile)	20	10	10	60	70
HADS Anxiety	5	0	2	7.5	11
HADS Depression	4	2	3	5.5	11

Functional activation analysis. Both the Stroop and Count task resulted in activation of areas within the frontoparietal control network, along with the SMA and pre-SMA, the lateral premotor cortex, and the cerebellum (see Figures 1, 2). In addition, there was

a predictable activation of the occipital cortex during the Stroop task. Outside of the visual cortex, we found no significant differences between activation patterns during the two tasks.

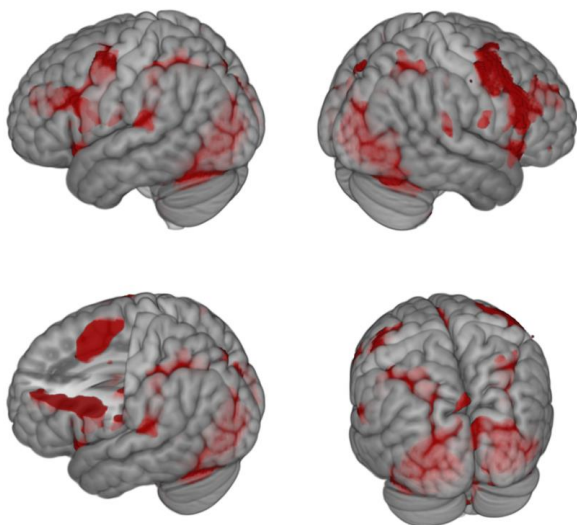


Figure 1. Activation map for the Stroop task ($p < .001$ uncorrected).

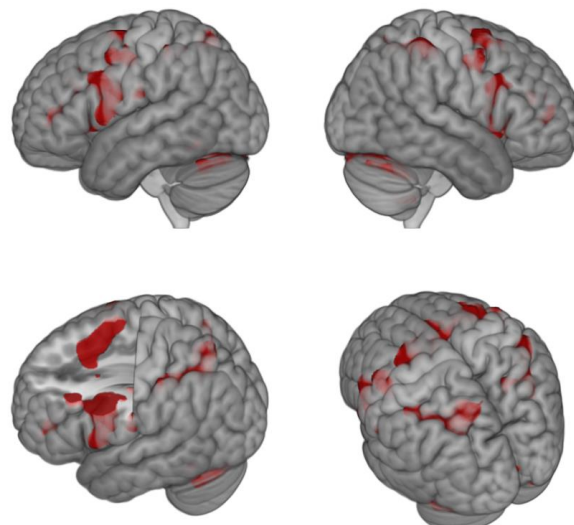


Figure 2. Activation map for the Count task ($p < .001$ uncorrected).

Table 2

Regions of interest within the frontal cortex (MNI coordinates of the center of the cluster).

	Stroop Task			Count Task		
	x	y	z	x	y	z
LDLPFC	-37	44	21	-41	42	9
RDLPFC	33	57	18	38	47	0
SMA	2	-1	61	0	-3	65
Pre-SMA	-8	16	48	-2	10	54
L lateral premotor cortex superior	-43	-3	58	-40	2	36
L lateral premotor cortex inferior	-56	9	12	-59	7	9
R lateral premotor cortex superior	51	4	50	34	4	61
R lateral premotor cortex inferior	51	27	26	55	4	41

On the basis of the activation analysis for both the Stroop and Count condition, we identified the following areas within the frontal cortex that were used as ROIs for the connectivity analysis: LDLPFC,

RDLPFC, SMA, pre-SMA, and left and right lateral premotor cortex (divided into superior and inferior parts due to elongated form of the clusters; Table 2).

To evaluate block consistency, a post hoc analysis was performed for the pre-SMA ROI (the selection of this area was influenced by the results of the

connectivity analysis, as outlined below). No significant differences were observed between the four task blocks (see Figures 3, 4).

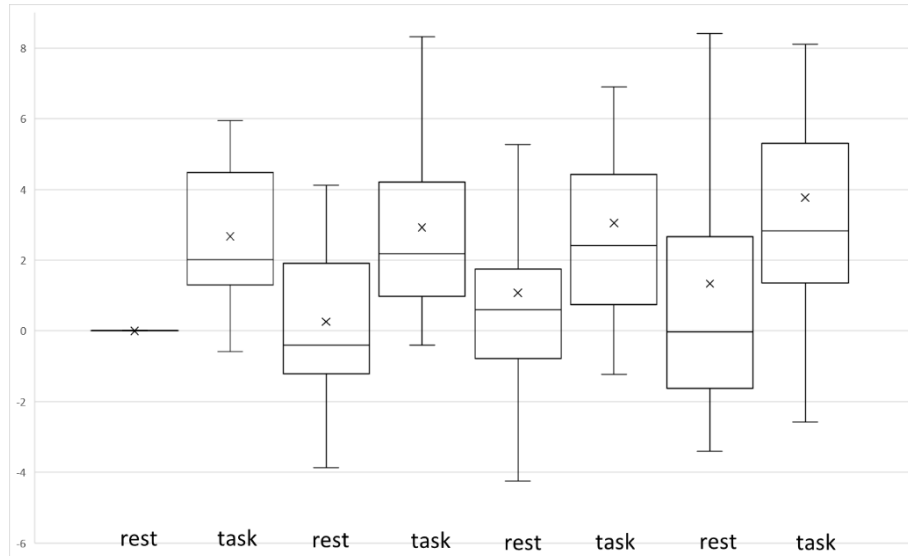


Figure 3. Time course of the activation of the pre-SMA during the Stroop task. Rest and task blocks are shown on the diagram; activation is expressed as the difference from baseline; boxes represent first to third quartile; whiskers represent minimal to maximal values; middle line represents the median; “x” sign represents the mean.

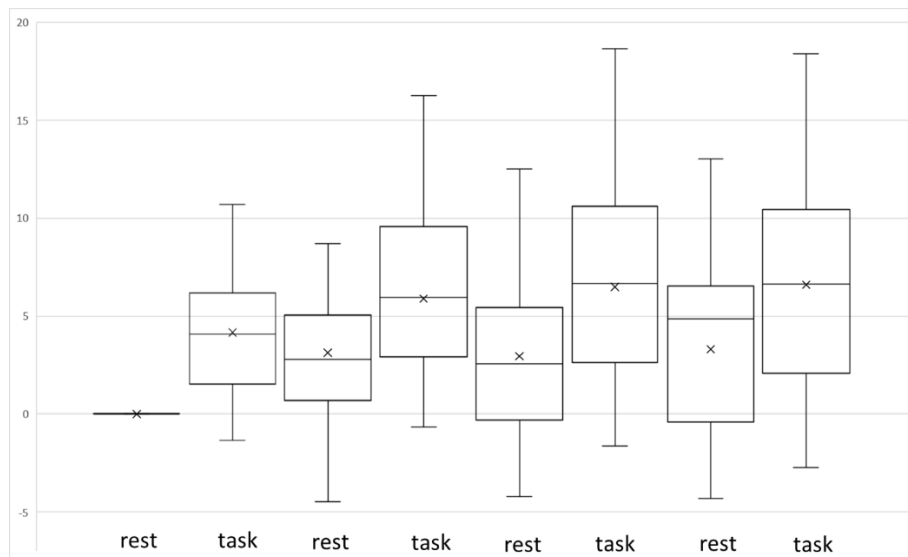


Figure 4. Time course of the activation of the pre-SMA during the Count task. Rest and task blocks are shown on the diagram; activation is expressed as the difference from baseline; boxes represent first to third quartile; whiskers represent minimal to maximal values; middle line represents the median; “x” sign represents the mean.

Functional connectivity analysis. Both the Stroop and Count task were associated with a widespread increase in connectivity in the pre-SMA, suggesting a major regulatory role of this area (Tables 3 and 4; Figures 5 and 6).

To a lesser extent, there was an increase in connectivity of other premotor areas: the left lateral premotor cortex during the Count task and the right lateral premotor cortex during the Stroop task. The counting task was also associated with functional coupling of the RDLPFC and the posterior cingulate cortex.

Table 3

Connectivity of the frontal cortex during the Stroop task.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	p (cluster, FDR-corrected)	p (peak, uncorrected)
		x	y	z			
Pre-SMA	L lateral occipital cortex	-32	-90	8	463	< .001	< .001
	R lateral occipital cortex	26	-88	8	213	.004	< .001
	R paracingulate gyrus, superior frontal gyrus	8	36	38	167	.016	< .001
R lateral premotor cortex superior	L postcentral gyrus	-42	-32	44	86	.02	< .001

Table 4

Connectivity of the frontal cortex during the Count task.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	p (cluster, FDR-corrected)	p (peak, uncorrected)
		x	y	z			
Pre-SMA	R angular gyrus, superior parietal lobule, lateral occipital cortex	40	-56	46	267	.005	< .001
	L superior temporal gyrus, planum temporale, middle temporal gyrus	-66	-26	2	190	.02	< .001
	R planum temporale, superior temporal gyrus	62	-12	4	164	.04	< .001
RDLPFC	R posterior cingulate cortex	14	-50	24	90	.03	< .001
L lateral premotor cortex superior	R insular cortex and putamen	30	14	-4	171	.04	< .001
L lateral premotor cortex inferior	R superior frontal gyrus	8	52	34	346	< .001	< .001

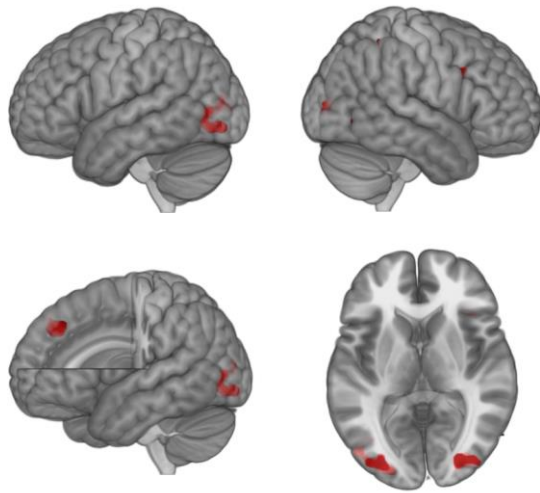


Figure 5. Connectivity map of the pre-SMA during the Stroop task (Stroop vs. rest, $p < .001$ uncorrected at voxel level).

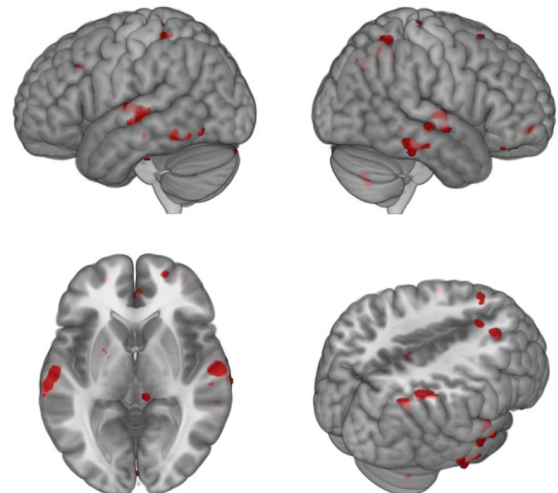


Figure 6. Connectivity map of the pre-SMA during the Count task (Count vs. rest, $p < .001$ uncorrected at voxel level).

Table 5

Connectivity of the frontal cortex during the Count task: Effects of BRIEF–MoCA value.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	p (cluster, FDR-corrected)	p (peak, uncorrected)
		x	y	z			
LDLPFC	R and L cuneal cortex	20	-72	20	712	< .001	< .001
	L superior frontal gyrus	-16	-2	68	148	.05	< .001
	L inferior frontal gyrus	-60	16	4	141	.05	.001
Pre-SMA	R cuneal cortex	14	-74	22	370	< .001	< .001
SMA	L intracalcarine cortex, lingual gyrus	14	-68	8	176	.02	< .001

Next, we evaluated the correlations between the BRIEF–MoCA value and task-based connectivity in the frontal areas. This analysis enabled us to reveal two main effects, both stemming from the counting task (Table 5). The ability to compensate for cognitive decline, measured by the BRIEF–MoCA value, correlated, first, with connectivity in the LDLPFC, and, second, with enrollment of the occipital cortex (Table 5; Figure 7). To exclude a possible effect of outliers, the main correlation effects were also explored visually (Figures 8A–8D).

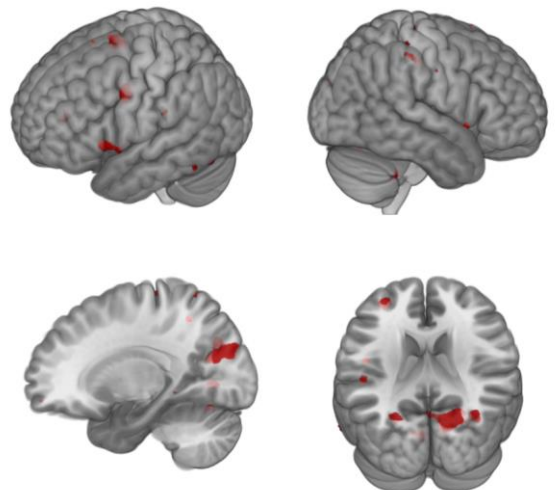


Figure 7. Connectivity map of the LDLPFC during the Count task: correlation with BRIEF–MoCA value (count vs. rest, effect of BRIEF–MoCA covariate, $p < .001$ uncorrected at voxel level).

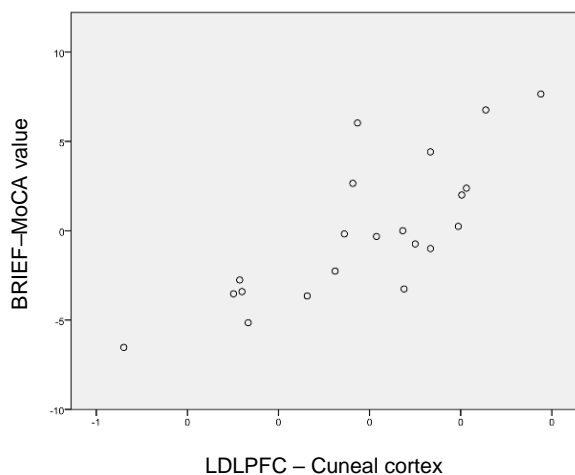


Figure 8A. Correlation of the BRIEF-MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the cuneal cortex.

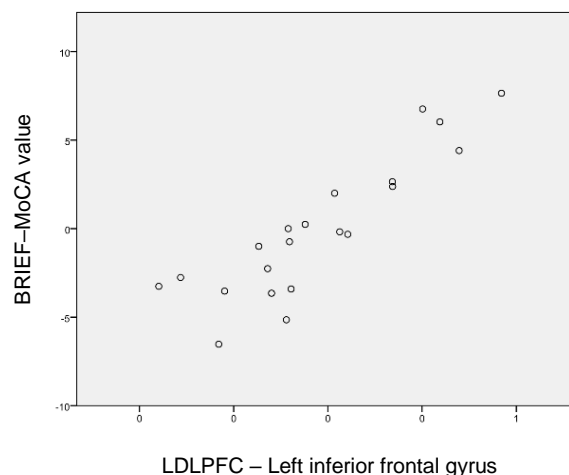


Figure 8B. Correlation of the BRIEF-MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the left inferior frontal gyrus (IFG).

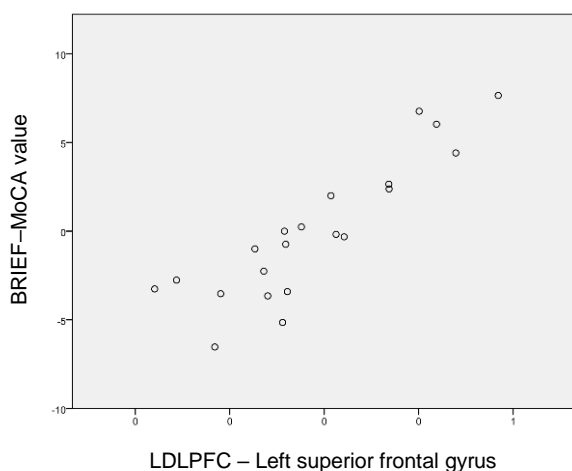


Figure 8C. Correlation of the BRIEF-MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the left superior frontal gyrus (SFG).

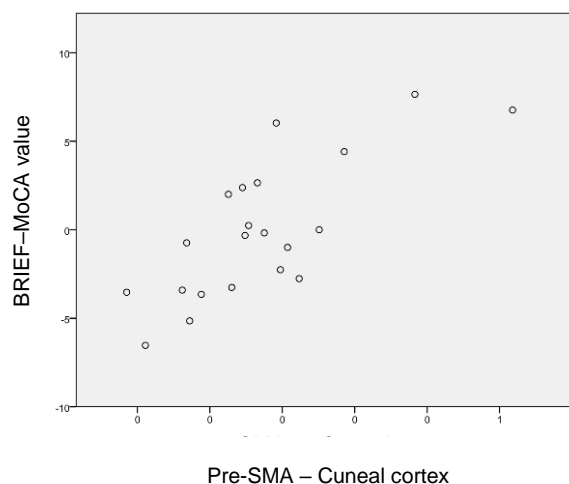


Figure 8D. Correlation of the BRIEF-MoCA value with connectivity in the frontal cortex during the Count task: between the pre-SMA and the cuneal cortex.

Discussion

While designing the study, we kept in mind a very practical goal—the possible application of fMRI maps for individualized neuromodulation. Despite the increasing clinical use of rTMS and tDCS, the complex problem of target individualization remains to be solved (Fitzgerald et al., 2009; Luber et al., 2017). First, the preference of the DLPFC over other functionally salient brain areas is not based on systematic investigation; the correctness of this empirical choice is unknown. Second, the standard method of DLPFC identification—positioning the coil 5 cm anterior to the motor “hotspot”—is very inaccurate; it allows correct positioning of the coil over the DLPFC in only 36% of cases (Ahdab, Ayache, Brugière, Goujon, & Lefaucheur, 2010). Third, the prefrontal cortex is known to be functionally heterogeneous; in fact, there are multiple areas within the DLPFC with different functional profiles (Cieslik et al., 2013; Fox, Liu, & Pascual-Leone, 2013). Mispositioning of the stimulation coil or electrode may interfere with the efficacy of neurostimulation.

To overcome the limitations related to individual variance in structural and functional brain anatomy, navigated TMS can be used. Neuronavigation allows a precise delivery of the stimulus based on neuroimaging, which results in an enhanced efficacy of rTMS, at least in motor applications (Bashir, Edwards, & Pascual-Leone, 2011). Functional neuroimaging can be used for identification of the salient areas. Both paradigms, Stroop and Count, being easy in comprehension and technically simple, may be implemented in clinical practice for the goal of pretreatment executive function mapping in cognitively impaired patients.

The pattern of activation elicited by both paradigms is typical for brain-level organization of task management (Figures 1, 2). The revealed areas within the frontoparietal control network—the DLPFC and the posterior parietal cortex—participated in high-order regulation. However, the main control region was the secondary motor cortex (lateral premotor, SMA, pre-SMA)—the stereotypical character of the paradigms allowed the delegation of control towards lower-order frontal areas (automatization). The secondary motor cortex is known to participate in various tasks including, but not limited to, motor paradigms (Lima, Krishnan, & Scott, 2016). While the SMA is responsible for movement generation and control, the pre-SMA supports more complex aspects of action, including action preparation and sequencing (Rizzolatti, Cattaneo, Fabbri-Destro, &

Rozzi, 2014; Sakai et al., 1999). In general, the revealed patterns of activation were close to the findings of earlier studies (Kaufmann et al., 2008; Naumczyk et al., 2017).

The results of the connectivity analysis support a major regulatory role of the pre-SMA. During the Stroop condition (Figure 5), increased connectivity was seen between the pre-SMA and the lateral occipital cortex, responsible for the synthesis of visual information, and between the pre-SMA and the anterior cingulate cortex, which has been linked to error detection (Bush, Luu, & Posner, 2000). A different pattern was observed during the Count task (Figure 6). Functional connectivity of the pre-SMA indicated that the task was accomplished with the use of verbal working memory: the superior temporal gyrus is involved in sound processing, and the angular gyrus is responsible for manipulations involving numbers in their verbal form, such as “one”, “two”, and “three” (Dehaene, Piazza, Pinel, & Cohen, 2003). As predicted, recruitment of the temporal cortex was seen predominantly on the left side. More surprising, the connectivity between the pre-SMA and the parietal cortex was lateralized towards the right angular gyrus. The right parietal cortex is known to be responsible for number processing that is spatially organized by numerical proximity (Zago et al., 2008). In the current task, the right angular gyrus might be involved in manipulation of the number line that represents a spatial structure.

From a practical point of view, executive tasks used in the fMRI settings are of questionable ecological value: it is unclear to what extent the observed brain functioning reflects its performance in real life. To address this limitation, we included a measure of everyday functioning—the BRIEF questionnaire—into our analysis. We propose that this score is a composite of cognitive capacities per se and of the ability to compensate for existing weaknesses. To clearly separate the second factor, which represents the main target of rehabilitation, we calculated the BRIEF–MoCA value and explored the correlation of this covariate with task-related connectivity in the frontal areas.

The covariate functional connectivity analysis (Table 5) revealed two main findings. First, the ability to compensate for cognitive decline, measured by the BRIEF–MoCA value, correlated with connectivity between the DLPFC and premotor areas, including the Broca area (Figure 7). The Broca area is involved in the transformation of the sensory representations of words forwarded from the temporal cortex into

articulatory code (Flinker et al., 2015). It also resolves the conflict between alternative representations in verbal and other domains (Hsu, Jaeggi, & Novick, 2017). In the Count task, this area might be responsible for the selection and encoding of the correct number in a situation of conflict (e.g., “four” vs. “three”) and, thus, has a major regulatory role. The LDLPFC exerts higher-order supervision over the secondary frontal areas, and identical top-down control might serve to compensate for cognitive decline in everyday life. Second, the BRIEF–MoCA value correlated with the enrollment of the medial occipital cortex: cuneal, intracalcarine, and lingual gyri (Table 5; Figure 7). This phenomenon may reflect compensatory strategies based on the recruitment of an additional modality—visual Arabic representations of numbers (i.e., “1”, “2”, “3”).

The results of our study may be implemented in clinical practice. In order to increase the efficacy of neuromodulation, the target area within the LDLPFC may be identified during pretreatment executive function mapping with the developed modified counting task. The utility of this individualized approach remains to be evaluated in further studies.

Author Disclosure

Authors have no grants, financial interests, or conflicts to disclose.

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