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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Probing the cognitive-motor organization of the left PMd using the N-back task: A neuroimaging study

Mathijs Deckx
Dante Nijs

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Koen CUYPERS

BEGELEIDER :
Mevrouw Sara Isabel DA SILVA MAGALHAES FERREIRA

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2023

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In this academic context, we would like to extend our sincere gratitude to Prof. dr. Koen Cuypers, who served as the study's promotor, and Ms. Sara Ferreira, who acted as the study's supervisor. Their valuable clinical expertise and guidance have greatly contributed to the progress and development of this research paper. Furthermore, we would like to express our deep appreciation to the University of Hasselt for providing the necessary resources and support throughout this study.

Research Context

Within the context of motor control, cognition, and brain, this research study primary focuses on unravelling the complex mechanisms involved in cognitive processes, the underlying brain structures, and functions. More specifically, the study aims to probe the cognitive-motor organization of the left dorsal premotor cortex using working memory assessment (N-back task).

This research study is conducted and written by graduate students in the context of obtaining a Master’s degree in Rehabilitation Sciences and Physical Therapy at the University of Hasselt. This duo master’s thesis contributes to an ongoing PhD research project set up by Ms. Sara Da Silva Magalhaes Ferreira under the supervision of Prof. dr. Koen Cuypers. All neuroimaging data used in this study were extracted from a public database called OpenNeuro. This means no additional data was acquired in the making of our master thesis. The different research questions for this study were determined by both students in consultation with Ms. Sara Da Silva Magalhaes Ferreira. Both students had equal input in conducting, writing and integrating feedback given by the supervisors.

Abstract

Background: Rostrocaudal gradients, found in specific brain regions can be analogue to cognitive-motor gradients. In this study, we will investigate three different regions within the left dorsal premotor cortex, namely the caudal, central, and rostral regions. These subdivisions are organized in this rostrocaudal/cognitive-motor manner.

Objectives: The aim of the study is to probe the cognitive-motor organization of the lPMd using the N-back task. The second research question discloses whether the capacity of an individual to adapt to different task demands correlates with the behavioral measures of accuracy rate and reaction time.

Methods: A public database (OpenNeuro) is used in this study containing neuroimaging data of the caudal, central, and rostral lPMd subregions from 43 individuals. This data was acquired by performing the N-back task for working memory assessment during two measurement sessions, one out-of-scanner and one in-scanner (fMRI). The activation of the different lPMd subregions was researched based on fMRI results while performing the N-back task with increasing task complexity. Various difficulties during the N-back task out of the scanner determined the behavioral measures (accuracy rate and reaction time).

Results and discussion: The results showed no significant activation difference between the subdivisions for the two task conditions but revealed a pattern that displays an increase in activation from caudal to rostral. We also found that there was no significant predictive character between the rostro-cognitive effect and behavioral measures.

Keywords: Left dorsal premotor cortex, rostrocaudal gradient, cognitive-motor organization, working memory, N-back task

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1. Introduction

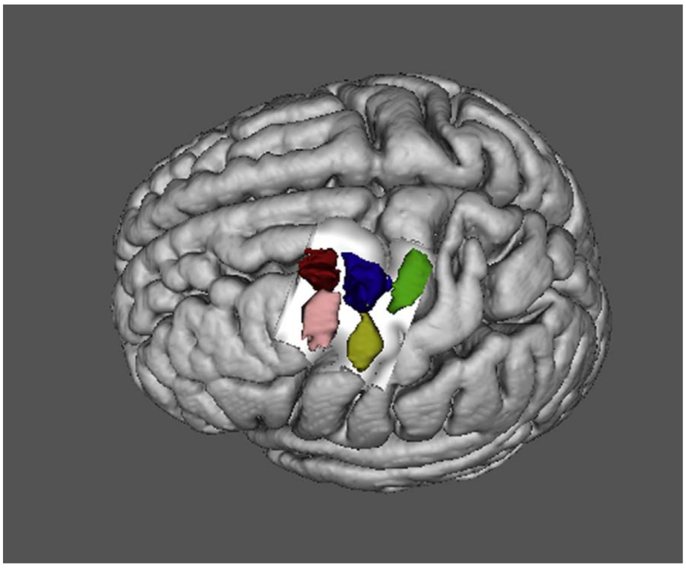
A growing number of studies have found the existence of a rostral to caudal subdivision of specific brain regions into functionally distinct components. Each subdivision within a specific brain region is designated with a name based on its specific location within that region. For instance, the term "caudal" refers to the lower part of the brain, while "rostral" is used to describe the front part. Interestingly, in frontal brain areas, such as the medial prefrontal cortex (mPFC), this rostrocaudal gradient is analogous to a cognitive-motor gradient (Genon et al., 2018a; Orban et al., 2015; Yeo et al., 2011). Thus, the rostral sub-parcels are mainly responsible for cognitive processes, whereas there is a gradual caudal specialization in motor-related functions.

Likewise, Genon et al. (2018a) recently suggested that the left dorsal premotor cortex (lPMd) presents a similar functional structure. A few years earlier, Genon et al. (2016) found the same results for the right dorsal premotor cortex (Genon et al., 2016). This structure was revealed using functional characterization to probe distinct subregions and their cognitive-motor organization along the rostral-caudal axis. The results indicated that the rostral, central, and caudal subregions demonstrated a cognitive-motor gradient. Precisely, the rostral subregion exhibited a significant association with higher-order cognitive functions. In contrast, the central subregion displayed a mixed pattern. Finally, the caudal subregion was related to motor functions.

By applying different statistical and meta-analytical techniques ranging from meta-analytic connectivity (MACM) and resting-state functional connectivity (RSFC) to probabilistic diffusion tractography (PDT), the authors were able to subdivide the lPMd into five subregions: caudal, central, rostral, ventral, and rostroventral, as can be seen in Figure 1 (Genon et al., 2018a).

Figure 1

Visual representation of lPMd subdivisions (Genon et al., 2018a, p. 405)



Note. Neuroimaging data revealed the presence of five distinct modules within the lPMd: red (rostral subregion), pink (rostro-ventral subregion), blue (central subregion), green (caudal subregion), and yellow (ventral subregion). From "The heterogeneity of the left dorsal premotor cortex evidenced by multimodal connectivity-based parcellation and functional characterization", by Genon et al., 2018a, NeuroImage, 170, p. 405, (https://doi.org/10.1016/j.neuroimage.2017.02.034).

These subregions not only have distinct functions but are also interconnected with different areas of the brain. Three of these five lPMd subcomponents are organized according to the referred cognitive-motor axis (Genon et al., 2018a). Specifically, the rostral module which serves cognitive functions such as working memory and spatial attention, was found to be functionally connected to the prefrontal cortex. Central region of lPMd is mainly responsible for motor planning by integrating visuospatial and somatosensory/motor functions and showed connectivity with the parietal lobe (Genon et al., 2018a). Caudal subregions of lPMd execute motor learning and several motor functions and show functional connections with the sensorimotor network (Bellec et al., 2010; Genon et al., 2018a; Glasser et al., 2016; Koechlin & Summerfield, 2007; Orban et al., 2015; Yeo et al., 2011).

As aforementioned, working memory is one of the cognitive processes that relies on the rostral portion of the lPMd (Bellec et al., 2010; Genon et al., 2018a; Glasser et al., 2016; Koechlin & Summerfield, 2007; Orban et al., 2015; Yeo et al., 2011). This higher-level cognitive system is able to store and manipulate information for a short period (Baddeley, 1986) and is a critical component by which information is held “on-line” to regulate human behavior when no external cues are available (Gevins & Smith, 2000; Goldman-Rakic, 1987). It provides the ability to preserve attentional focus, create task-related mental images, and suppress distracting events (Engle et al., 1999).

Working memory is broadly assessed using the N-back task, a task during which the participants are instructed to monitor a sequence of stimuli successively. For each stimulus, the participant must acknowledge whenever the current stimulus is equivalent to the one given N trials back. When performing the N-back task, manipulating the value of N or the stimulus duration, achieves different levels of task complexity. At higher levels of difficulty, the task requires more cognitive load due to the increased information held “on-line”. In addition, increased motor demands are vital for less frequent match responses and result in more perceived effort and response time, compared with more frequent match responses. Thus, the level of cognitive and motor input required to perform the N-back task increases with higher levels of difficulty (Owen et al., 2005).

Recent findings from Genon et al. (2018a) show the recruitment of the rostral subregion of the lPMd, during working memory performance and the involvement of the caudal part during motor performance (Genon et al., 2018a). Despite these findings, there is yet to exist a comprehensive study probing the functional differentiation of lPMd into the structured subregions by looking into their differential activation under different conditions of the same task that vary in the level of cognition and motor ability required. Therefore, we propose to do that using the N-Back task, as previous research has shown that the 0-Back condition of the N-back task cognitively simply demands attentional monitoring of the goal, while 2-Back involves both working memory and attentional monitoring to supervise the stimuli (Li et al., 2021). That is, the higher the task complexity (i.e., the higher the number of stimuli to be temporally memorized), the more cognitively demanding it is. Moreover, we will investigate whether individuals with the capacity to properly modulate brain activity in the lPMd as a function of task complexity present better task performance, as measured by the mean accuracy rate (AR) and reaction time (RT).

To summarize, in our study we aim to (1) probe whether lPMd is functionally subdivided into three subregions that are involved in cognitive processes at different levels by looking into how distinctively activated each subregion is during 1-Back and 2-Back and (2) understand whether the capacity of an individual to adapt to the different task demands by recruiting different lPMd subregions is related to better task performance. We hypothesized whether involvement of the rostral and central subregions of the lPMd will increase when task complexity increases. In contrast to the rostral region, the caudal region is hypothesized to be less involved during the 2-Back task condition. In other words, activation of the caudal region decreases with working memory tasks of higher difficulty. Finally, we hypothesize that participants who show a higher activation of the rostral and central regions combined with a lower activation of the caudal region when task complexity increases, would score higher in AR and have faster RT.

2. Methods

All neuroimaging data used in this study were extracted from a public database called OpenNeuro at https://openneuro.org/datasets/ds003849/versions/1.0.0. This data was originally acquired by Boroshok et al. (2022) for their research paper: “*Individual differences in frontoparietal plasticity in humans*” (Boroshok et al., 2022). Therefore, the article by Boroshok et al. (2022) was the main source of information for the methodology employed in our study.

2.1. Participants

The recruitment of the participants was performed by using the University of Pennsylvania study recruitment system and advertisements at universities and community colleges. Only participants between the ages of 18 and 25 years who speak fluent English were allowed to participate in the study. Exclusion criteria consisted of a history of neurological or psychiatric disorders, current or recent illegal substance use, learning disabilities, and magnetic resonance imaging (MRI) contraindications (Boroshok et al., 2022).

MRI scans were conducted for 61 subjects in total, 15 of them were excluded from the study for several reasons (e.g., poor fMRI N-back task performance, falling asleep during the N-back scan, etc.) (Boroshok et al., 2022). Additionally, three participants were excluded from this study because of problems with exporting the images from OpenNeuro. The final sample is composed of 43 individuals.

2.2. Study design and procedure

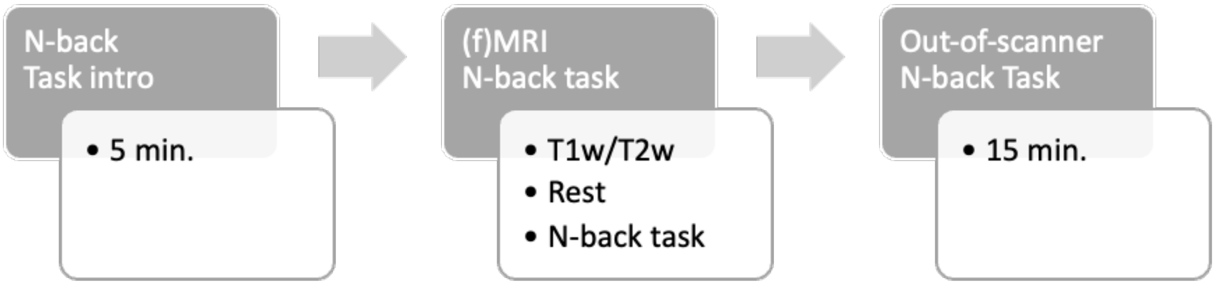
2.2.1. Study design

To start with, the study protocol began with a five-minute introductory session explaining the N-back task. Next, an anatomical MRI scan was taken to have baseline T1-weighted (T1w) and T2-weighted (T2w) data at rest to map the anatomical part of the brain. These structural scans were followed by a resting-state functional MRI (fMRI) scan to look at the functional processes in the lPMd in a resting state of the participant. The last scan was an fMRI scan to have a closer view of the functional processes in the subregions of the lPMd while performing the N-back task. Subsequently, participants performed a 15-minute N-back task outside the scanner where the behavioral data was acquired (Figure 2) (Boroshok et al., 2022).

To summarize, two different measurement moments of the N-back task were scheduled; the N-back procedure out of the scanner and the N-back procedure during fMRI (Boroshok et al., 2022). While it might seem redundant to gather behavioral data outside the scanner when you could also acquire this information during fMRI, this could be explained by several reasons. Collecting behavioral data inside the scanner may affect the accuracy and reaction time of participants. The increased levels of stress and distractions endured during fMRI or the ability to adequately focus on the task at hand, could alter the results. Next, by comparing behavioral data obtained outside the scanner with brain activation data during fMRI, researchers can examine the relationship between the two. This approach could reveal the relationship between individual differences in behavioral performance and differences in brain activation patterns.

Figure 2

Schematic representation of study design



Note. The study protocol started with a brief initiation to the N-back working memory task, followed by a comprehensive MRI session that included structural and functional scans. Thereafter, a 15-min out-of-scanner session assessed individual performance on the N-back task (accuracy and response time) (Boroshok et al., 2022).

2.2.2. Procedure: N-back task - Working memory assessment

Numerous modified versions of the N-back task procedure have been developed to explore the neural basis of working memory processes and to address specific research questions. Across studies, a wide variety of stimuli presented through different input modalities have been applied, including visual, auditory, and olfactory, all of which engage different processing systems and impose different cognitive demands (Owen et al., 2005).

Commonly used and applied in this study is the auditory N-back task variant, where the participants are required to monitor a sequence of auditory stimuli successively. For each stimulus, participants must acknowledge whenever the current stimulus is equivalent to the one given N trials back (Owen et al., 2005). Two different measurement moments of the N-back task were scheduled; the N-back procedure outside the scanner and the N-back procedure during fMRI (Boroshok et al., 2022).

To start with, the N-back procedure inside the scanner consisted of two cognitive conditions, 1-Back and 2-Back, for 12 blocks. All participants executed the fMRI N-back procedure containing 12 trials in each of the four 30-second-long blocks. At the onset of each block, the current N-back condition was displayed in the middle of a black screen for a duration of 2500 ms, followed by the appearance of response options "YES" and "NO". Next, a brief audio clip featuring a single consonant was presented for 500 ms. Participants were assigned a 2000 ms window to indicate their response via button press on a standard keyboard, where "F" and "J" corresponded to "YES" and "NO" responses, respectively. A rest period of 10 seconds separated each block. Feedback was provided to participants, with accurate and inaccurate responses prompting the highlighting of the correct response option in green or red, accordingly (Boroshok et al., 2022).

Afterwards, the N-back task outside the scanner was performed consisting of 24 trials in each of the 12 blocks. Stimuli were randomly selected from a group of eight consonants ('C,' 'D,' 'G,' 'K,' 'P,' 'Q,' 'T,' and 'V'). During the outside the scanner procedure, equivalent to inside the scanner, participants were presented with consonant stimuli for a duration of 500 ms and provided with a response window of 2000 ms to indicate their response (Boroshok et al., 2022). This standard timing protocol is applied to ensure consistency and enable comparison across different procedures. To evaluate individual performance, two primary behavioral measures were evaluated during the out of the scanner procedure: (1) the task AR across trials, as characterized by the percentage of correctly answered trials, and (2) the RT across trials (Boroshok et al., 2022).

2.3. Neuroimaging data acquisition and processing

2.3.1. Data acquisition

“The neuroimaging was done at the Centre for Magnetic Resonance Imaging & Spectroscopy at the University of Pennsylvania by using a Siemens MAGNETOM Prisma 3T MRI Scanner (Siemens, Erlangen, Germany) with a 32-channel head coil” (Boroshok et al., 2022).

The imaging protocol consisted of T1w and T2w structural scans, a resting-state scan and a task-related fMRI scan while performing the N-back task. They started with the structural scans with volumetric navigators: a whole-brain T1w multi-echo at a high resolution (MEMPRAGE, TR = 2530 milliseconds; TEs = 1.69, 3.55, 5.41, 7.27 milliseconds; flip angle = 7°; resolution = 1 mm isotropic) and T2w (T2SPACE, TR = 3200 ms; TE = 406 ms; resolution = 1 mm isotropic; turbo factor: 282) (Boroshok et al., 2022).

While performing these structural scans, participants watched a nature documentary. Immediately after the structural scans the participants went through a five-minute run of resting-state fMRI where the participants looked at a fixed cross (TR = 2000 ms; TEs = 30.20 ms; flip angle = 90°; resolution = 2 mm isotropic). At last, a task-related fMRI scan during the N-Back task was performed (TR = 2000 ms, TE = 30.2 ms, flip angle = 90°, voxel size = 2.0 × 2.0 × 2.0 mm, matrix size = 96 × 96 × 75, 75 axial slices, 170 volumes, field of view = 192 mm). To reach a steady-state MRI signal, the first four volumes of each scan were automatically deleted for both echo planar imaging (EPI) sequences (Boroshok et al., 2022).

2.3.2. Image preprocessing

In this study, fMRIPrep 20.2.7 workflow (fMRIPrep, 2016-2023) preprocessed the data. The fMRIPrep workflow is a tool used to prepare the neuroimages by combining multiple tools of popular software packages such as: FMRIB Software Library (FSL v5.0.9), Advanced Normalization Tools (ANTs v2.1.0.), FreeSurfer (v6.0) and Analysis of Functional NeuroImages (AFNI) (Avants et al., 2014; Cox, 1996; FMRIB Analysis Group, 2004; Laboratory for Computational Neuroimaging, 2017). The goals of preprocessing are to refine the different data variations and create convenient and homogenous output for researchers to work with (Boroshok et al., 2022; NiPreps, 2023).

The preprocessing phase approached the anatomical data and functional data in a different way. The anatomical data containing T1w images went through different correction phases. To clarify, a correction phase often applied to T1w images, plays a crucial role in reducing artifacts, enhancing image quality, and facilitating reliable interpretation and analysis of MRI data. The initial data was corrected for intensity non-uniformity (INU) ANTs 2.3.3. (Avants et al., 2014). Next, data was also compared to a T1w reference which was skull-stripped with a

Nipype implementation of the antsBrainExtraction.sh workflow (Avants et al., 2014). After these steps, the cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) were segmented by using FSL 5.0.9. (FMRIB Analysis Group, 2004). Thereafter, two standard spaces were created (MNI152NLin2009cAsym, MNI152NLin6Asym) by volume-based normalization. AntsRegistration (Avants et al., 2014) performed the nonlinear regression analysis, employing both T1w reference and T1w template using brain-extracted versions (Boroshok et al., 2022).

The functional data also went through a preprocessing phase starting by distortion correction (Syn distortion correction). After this, the blood oxygen level dependent (BOLD) reference was co-registered by a configuration of nine degrees of freedom to the T1w reference using flirt (FSL v5.0.9) with the boundary-based registration cost-function. Before any spatiotemporal filtering was done, head-motion parameters were estimated with respect to the BOLD reference by using mcflirt (FSL v5.0.9). After that, BOLD runs were slice-time corrected to 0.95s by using 3dTshift from AFNI 20160207. “The BOLD time series were resampled onto their original native space by applying a single, composite transform to correct for head motion and susceptibility distortions. Afterwards the BOLD time series were resampled again into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space” (Behzadi et al., 2007).

Next, Independent component analysis (ICA-AROMA) automatically removed motion artifacts. This automatic elimination process was conducted on the preprocessed BOLD time series in MNI space. Prior to this, non-steady-state volumes were removed, and spatial smoothing was applied using a 6mm full-width half-maximum isotropic Gaussian kernel. Corresponding non-aggressively denoised runs, aiming to strike a balance between noise reduction and preservation of the underlying data characteristics, were produced after such smoothening. A corresponding confounds file was made to collect the aggressive noise-regressors, head-motion estimates which were calculated in the correction step and others. After the preprocessing phase, data was checked and denoised using CompCor, a denoiser toolbox (Behzadi et al., 2007) which resulted in the removal of the confound regressors (Boroshok et al., 2022).

2.3.3. Image processing

After the pre-processing, a general linear model was conducted using SPM12, which was followed by the calculation of the whole-brain BETA values for the contrast 2-Back - 1-Back. A BETA value represents the mean increase in the dependent variable when the independent variable increases by one standard deviation, assuming all other independent variables are held constant. Then, mean BETA values for each region of interest (ROI) (central, rostral and caudal) were estimated by masking each individual's pre-processed BOLD on MNI space with the lPMd subregions defined by Genon et al. (2018a), and available at EBRAINS (Genon et al., 2018b).

2.4. Regions of interest (ROIS)

This study is based on the findings of Genon et al. (2018a) to recreate the different regions of interest (ROIs). The article of Genon et al. (2018a) focused on three different methods to define several regions of the lPMd: meta-analytic connectivity modelling (MACM), resting-state functional connectivity (RSFC) and probabilistic diffusion tractography (PDT). MACM was based on the data of the Brainmap database to focus on task-based functional connectivity. For PDT and RSFC the open-access database "Rockland" (Genon et al., 2018a) was used to obtain diffusion-weighted imaging and resting-state data. For reader's information, the caudal region related to bilateral primary sensorimotor areas, cerebellum, and secondary somatosensory cortex. In turn, the rostral area relates to bilateral middle frontal cortex, the inferior parietal cortex and precuneus. Finally, the central area was strongly connected with the right supramarginal and inferior gyri and with the bilateral superior parietal cortex. By combining these three different methods, Genon et al. (2018a) shaped masks of the different lPMd subregions and configured them by using the SPM Anatomy Toolbox in cytoarchitectonic maps. In this study, these masks were used to calculate the exact placement of the lPMd regions. By using this method, it is possible to assess brain activation in those specific calculated regions and compare them at the group level.

2.5. Statistical analysis

All statistical analyses were accomplished using JMP Pro software version 16.0.2 (JMP Statistical Discovery LLC, 1989-2023). In total, there are two distinctive research questions aiming to (1) probe whether lPMd is functionally subdivided into three subregions that are involved in cognitive processes at different levels by examining the distinct activation of each subregion is during 1-Back and 2-Back and to (2) understand whether the capacity of an individual to adapt to different task demands by recruiting different lPMd subregions is related to better task performance.

To start with analyzing how distinctively activated each subregion is, a contrast of the entire brain's activation was measured which resulted in a brain map of positive values (2-Back > 1-Back) and negative values (2-Back < 1-Back). From this entire brain map, mean BETA values were measured for each lPMd subregion which were used in the analysis. In order to formulate an answer to the first research question, we conducted repeated measures ANOVA (JMP Statistical Discovery LLC, 1989-2023). The ρ-value of 0.05 or lower was considered statistically significant.

The null hypothesis expects an equal change in lPMd subdivision activation between the two task conditions. In other words, involvement of the rostral, central, and caudal subregions will vary when task complexity increases but no significant difference would be perceived between subregions. Our alternative hypothesis expects a significant difference in activation between the different lPMd subregions being the rostral, central, and caudal components. Based on the rostro-caudal organization theory, we expect a greater involvement of the rostral subregion when performing the 2-back condition because of higher task complexity, thus requiring more cognitive demand. In the results section, this difference in activation between the lPMd subdivisions was analyzed using a post-hoc test in ANOVA. Further, we hypothesize no significant difference in activation of the central subregion and decreased caudal importance with higher task complexity.

Subsequently, the second research question regarding the relation between the capacity of an individual to adapt to different task demands by recruiting different lPMd subregions and task performance, was analyzed using multiple regression analysis (JMP Statistical Discovery LLC, 1989-2023). This regression aims to model the relationship between the dependent variables; AR or RT and the regressors (i.e., independent variables); continuous BETA values of the various lPMd subregions. Multiple regression results in an equation used to predict values of AR or RT based on the values of the different lPMd subdivision activations.

The null hypothesis suggests that there is no significant relationship between the dependent variable (AR and RT) and the independent variables (rostral, central, and caudal and the association between the three different regions (caudal*central*rostral) BETA values). To put it differently, the null hypothesis of the multiple regression analysis posits that alterations in the independent variables do not yield any consequential impact on the dependent variable, as the regression coefficients for all independent variables are zero ($\rho = 0$). The alternative hypothesis states that there is a significant association present between variables, which can be positive or negative ($\rho \neq 0$, $\rho < 0$, $\rho > 0$). The analysis was accomplished using data 2 back - 1 back of the three various lPMd subregions and the association as independent variables. The four different independent variables which have been described before, were then related with RT and AR in two separate analyses.

3. Results

The analyses included continuous BETA values of the various lPMd subregions, AR, and RT results from 43 adults who completed one fMRI scan and one outside the scanner N-back task session (Figure 2). All statistical analyses were performed with JMP pro software version 16.2.0 (JMP Statistical Discovery LLC, 1989-2023). Using this statistical software, we aimed to answer the following research questions: (1) probing the activation of lPMd's rostral, central, and caudal subdivisions during working memory task conditions with increasing difficulty (1-Back and 2-Back) and (2) understanding whether the capacity of an individual to adapt to the different task demands explain the AR and RT.

Influence of task complexity on lPMd subdivision activation

To begin with, we conducted repeated measures ANOVA (mixed model) in JMP (JMP Statistical Discovery LLC, 1989-2023) using the BETA values as stated before. In mixed model ANOVA, the activation contrasts 2-Back - 1-Back were used as dependent or Y-variable. On the other hand, a categorical variable was produced to allocate the BETA values to their correspondent lPMd subregion.

We found that there is no significant effect (F = 1.986; p = 0.142) of lPMd subdivisions. This means that there is no significant difference in average activation between the different lPMd subregions being the rostral, central, and caudal. After executing the post-hoc test to compare means between subdivision groups (Tukey HSD all pairwise comparisons in JMP) we did notice a higher mean estimate of the rostral subregion compared to central and caudal regions (Table 1, Figure 3). The Least Squares Means table and plot (Table 1, Figure 3), gave us more insight as to the mean average for each of the lPMd subregions. A pattern is visible, as shown in Figure 3, which emphasizes the increase in average activation from caudal to rostral. Put differently, the rostral subregion is more involved during working memory tasks with higher difficulty compared to the caudal and central areas.

Table 1

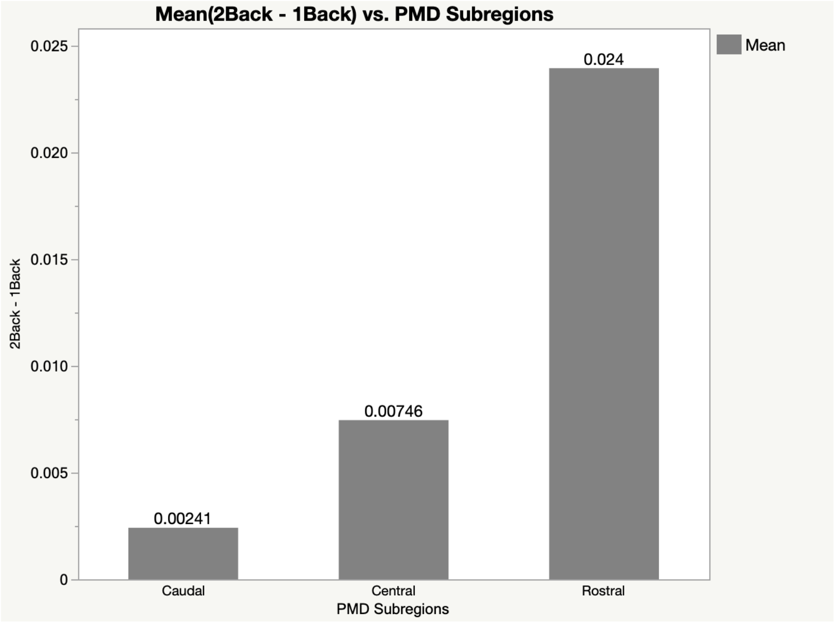
lPMd subregions LS Means table

lPMd subdivision	Estimates	Std Error	DF	Lower 95%	Upper 95%
Caudal	0.00241469	0.00799439	126	- 0.0134060	0.01823535
Central	0.00745961	0.00799439	126	-0.0083611	0.02328028
Rostral	0.02395480	0.00799439	126	0.0081341	0.03977547

Note. This table shows the average mean estimates for all dorsal premotor subdivisions (caudal, central, and rostral). Next columns refer to standard error (Std Error) and degrees of freedom (DF). Lastly, a lower and upper 95% confidence interval are displayed.

Figure 3

lPMd subregions LS Means plot



Note. In this figure, the Y-axis demonstrates the mean 2Back - 1Back BETA value. The caudal, central, and rostral lPMd subregions are displayed on the X-axis. As stated before, a pattern is visible which emphasizes the increase in average activation from caudal to rostral (JMP Statistical Discovery LLC, 1989-2023).

Relationship between task complexity adaptability and behavioral measures

We assessed the strength of the relationship between the AR, RT of the N-back task, and the independent variables (rostral, central, and caudal and the association between the three different regions (caudal*central*rostral) BETA values). In other words, we were looking for the strength of the relationship between the interactive effect of the three different subdivisions of lPMd which was seen when task difficulty increased (Table 1, Figure 3) and RT or AR. RT and AR values were obtained from the N-Back task which was performed outside the scanner in three different task conditions (2-Back, 3-Back, and 4-Back). Raw data were normalized using the following formula: SNi = [(Si-Smin)/(Smax-Smin)]. In this formula SNi corresponds to the normalized score of the Si value (raw score). Smin and Smax refers to the minimum and maximum values considering all the participants. After the normalization step, an average score for AR and RT was calculated, per participant, based on the scores obtained on all three out-of-scanner task conditions. The statistical analysis was done by using multiple regression aiming to model the relationship between the dependent variables; AR or RT and the regressors (i.e., independent variables); BETA values of the various lPMd subregions (caudal, central, and rostral).

First, in the analysis of the variable RT was found that there is a very low prediction rate of the different lPMd regions based on RSquare, F-ratio and significance level. In the analysis we found a RSquare (RSquare = 0.070655) which reflects a very low predictive function. The next results of the complete analysis showed no significant relationship or predictive rate of the different lPMd regions (F = 0.7223; df = 4; p = 0.5821). More in detail and based on the results of the effect test of the analysis we could conclude that the caudal part (F = 2.1873; p = 0.1474), central part (F = 0.0060; p = 0.9387), rostral part (F = 0.0597; p = 0.8083) and the association between the three parts (F = 0.0024; p = 0.9610) had no significant predictive effect on RT (JMP Statistical Discovery LLC, 1989-2023).

Table 2

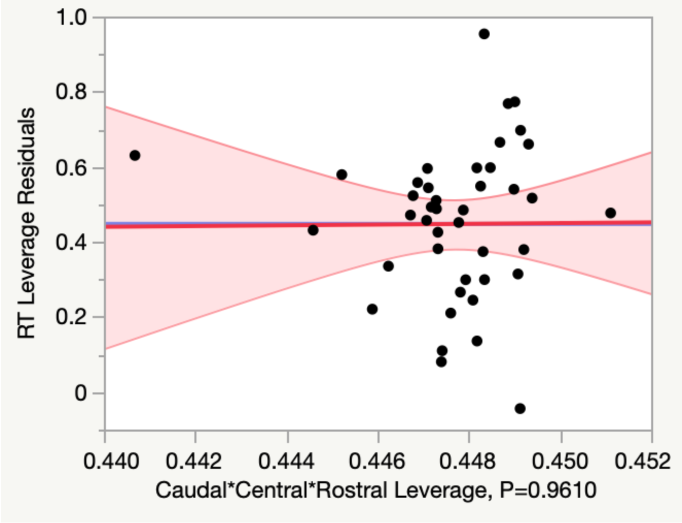
Effect test for response time

lPMd subdivision	Sum of Squares	DF	F-Ratio	Prob > F
Caudal	0.09860984	1	2.1873	0.1474
Central	0.00027022	1	0.0060	0.9387
Rostral	0.00269199	1	0.0597	0.8083
Caudal*Central*Rostral	0.00010910	1	0.0024	0.9610

Note. This table shows the effect test for RT and the independent variables (rostral, central, and caudal and the association between the three different regions (caudal*central*rostral) BETA values). Next columns refer to the Sum of Squares and degrees of freedom (DF). Finally, the F-ratio and P-value are displayed.

Figure 4

*Caudal*Central*Rostral RT leverage plot*



Note. This figure is a visual representation of the relationship between RT and the intercept between the three subregions (caudal*central*rostral). The x-axis represents the associational values of the three subdivisions combined. The red line resembles the line of best fit (i.e., best approximation of used data).

Secondly AR was statistically examined. The prediction capacity and strength of the relationship of the different regions and their effect with the AR of the N-Back task were different than in the RT analysis. In the analysis we found a RSquare of 0.262882. The next results of the complete analysis showed a significant relationship or predictive rate of the different lPMd regions globally (F = 3.3880; df = 4; p = 0.0182). When we looked more in detail to the different results, we could conclude that the caudal part (F = 0.6998; p = 0.4081), central part (F = 1.2248; p = 0.2754) and the association between the three parts (F = 2.4761; p = 0.1239) had no significant predictive capacity on the AR. The only exception is the rostral part (F = 13.2748; p = 0.0008) which shows a higher and significant predictive effect on the AR as shown in Table 3 and Figure 5 (JMP Statistical Discovery LLC, 1989-2023).

Table 3

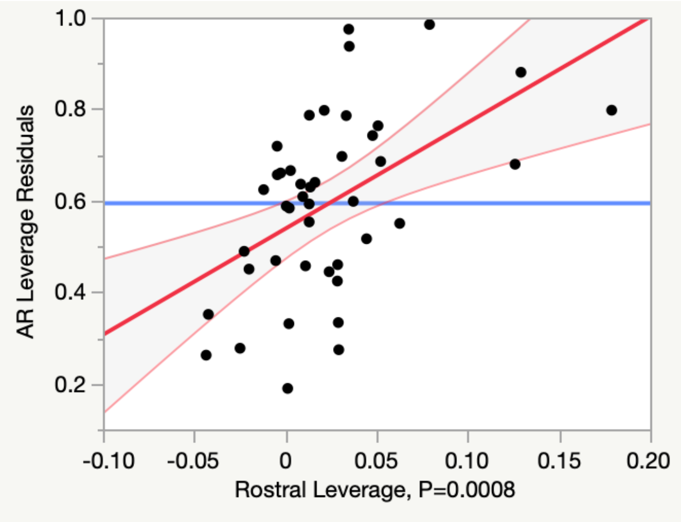
Effect test for accuracy rate

Source	Sum of Squares	DF	F-Ratio	Prob > F
Caudal	0.02156299	1	0.6998	0.4081
Central	0.03773917	1	1.2248	0.2754
Rostral	0.41211209	1	13.3748	0.0008*
Caudal*Central*Rostral	0.07629462	1	2.4761	0.1239

Note. This table shows the effect test for AR and the independent variables (rostral, central, and caudal and the association between the three different regions (caudal*central*rostral) BETA values). Next columns refer to the Sum of Squares and degrees of freedom (DF). Finally, the F-ratio and P-value are displayed. Unlike other lPMd subregions, the rostral part shows a higher and significant predictive effect on the AR (p = 0.0008).

Figure 5

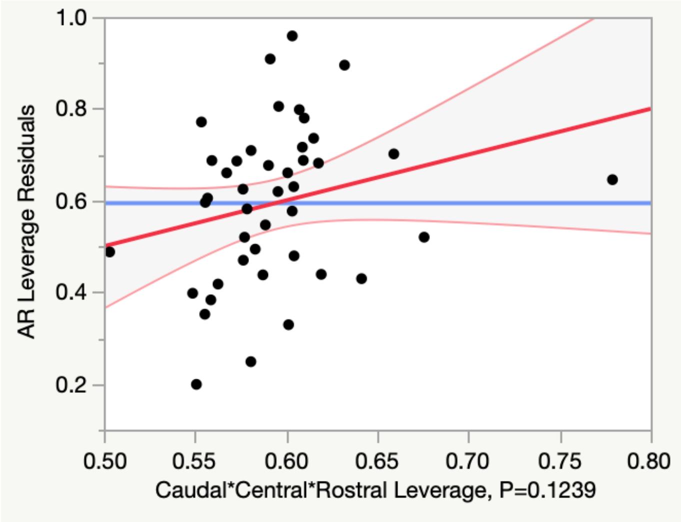
Rostral AR leverage plot



Note. This figure is a visual representation of the relationship between AR and the intercept between the rostral subregions. The red line resembles the line of best fit (i.e., best approximation of used data). Unlike other lPMd subregions, the rostral part shows a higher and significant predictive effect on the AR (p = 0.0008).

Figure 6

*Caudal*Central*Rostral AR leverage plot*



Note. This figure is a visual representation of the relationship between AR and the intercept between the three subregions (caudal*central*rostral). The red line resembles the line of best fit (i.e., best approximation of used data).

Behavioral difference in the different task conditions

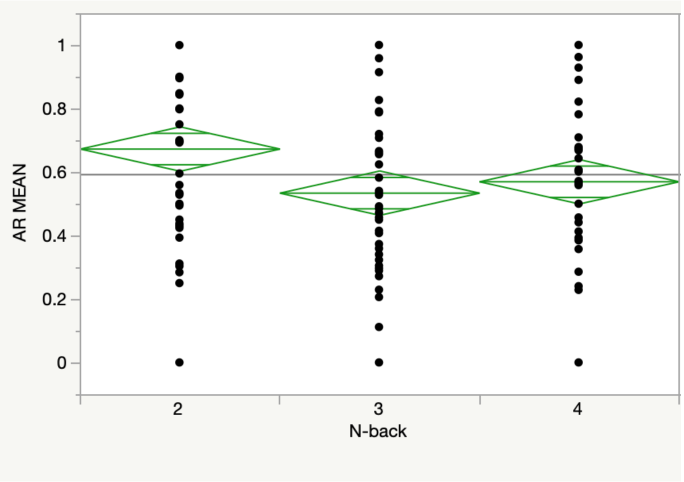
To formulate an objective conclusion of the results which were discussed before, it is crucial to analyze the differences in AR and RT between the different task conditions (2-Back, 3-Back, and 4-Back). To analyze these differences, repeated measures ANOVA was conducted (JMP Statistical Discovery LLC, 1989-2023).

After analyzing the differences in AR between 2-Back, 3-Back, and 4-Back conditions, an overall significant difference in mean AR was found between groups (p = 0.0177). After a global significant mean difference was found, a post-hoc (Tukey HSD) analysis was executed. This analysis showed that only mean difference between 2-Back and 3-Back was significantly different (p = 0.0171). Other pairs (2-Back and 4-Back, p = 0.1019; 3-Back and 4-Back, p = 0.7534) were not significantly different.

Secondly, the procedure was repeated for RT. Consistent outcomes were observed in this analysis, mirroring those obtained in the AR analysis. An overall significant difference in mean RT between the groups was identified (p = 0.0012). Following post-hoc tests, there was only a significant mean difference found between the 2-Back condition and 4-Back condition (p = 0.0008). The remaining pairs exhibited no statistically significant difference (2-Back and 3-back; p = 0.1384, 3-Back and 4-Back; p = 0.1600).

Figure 7

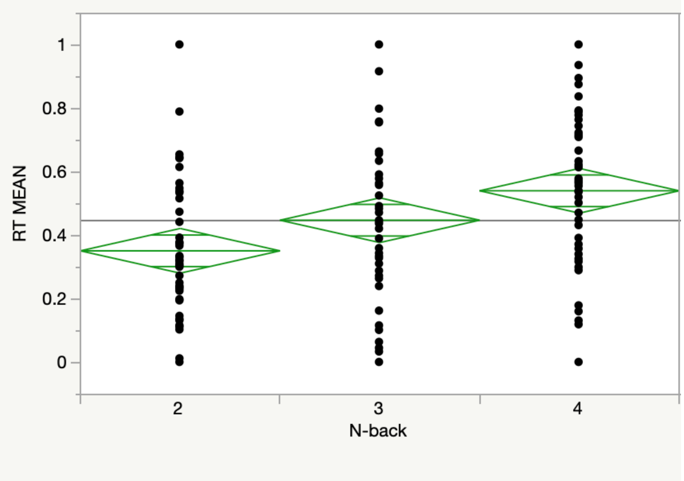
AR and task complexity comparisons plot



Note. This figure is a visual representation of the difference in mean AR (Y-axis) during three different N-back conditions (X-axis).

Figure 8

RT and task complexity comparisons plot



Note. This figure is a visual representation of the difference in mean RT (Y-axis) during three different N-back conditions (X-axis).

4. Discussion

In this research paper, we studied the involvement of the rostral, central, and caudal subdivision of lPMd in cognitive processes at different levels by looking into how distinctively activated each subregion is during 1-Back and 2-Back. We also investigated whether the capacity of an individual to adapt to the different task demands by recruiting the different lPMd subregions, is related to better N-back task performance.

To start with, the first statistical analysis revealed the mean activation values (2-Back - 1-Back) for each of the lPMd subregions. No significant effect was found for the different subdivisions meaning that the average activation was not significantly different between subregions with increasing task complexity. Regardless of these findings, a pattern was observed showing an increase of average activation from caudal to rostral (Figure 3), implying the importance of the rostral subregion during higher task difficulty. Although no significant results were found, these findings do show that the rostral component does execute higher cognitive functions compared to the other regions. In the paper of Abe and Hanakawa (2008), probing the underlying motor and cognitive functions of the dorsal premotor cortex, similar results have been demonstrated as the cognitive components of motor behavior are more predominantly processed in the rostral PMd sector than the caudal PMd sector while both sectors appear to contribute to execution of complex movements (Abe & Hanakawa, 2008).

Likewise, an exploratory lesion study by Badre et al. (2009) demonstrated the first direct support for rostral to caudal hierarchy. Lesions in caudal frontal areas of the brain resulted in deficits in more-abstract action selection. However, Lesions in rostral frontal areas did not result in deficits in more-concrete action selection. Abstract action selection is required when the motor task does not specify what particular sequence of movements are necessary (Badre et al., 2009). For those reasons, we can assume this trend is associated with the cognitive-motor gradient. These results may correspond to the findings of Genon et al. (2018a), suggesting that the lPMd rostrocaudal gradient is analogous to the cognitive-motor gradient. In our study, a working memory assessment task (N-back) was used to probe the cognitive-motor organization of the lPMd. Future research could also include a motor task to investigate whether caudal lPMd activation increases with greater motor output. Such a motor task could probe the cognitive-motor axis in the opposite direction and reveal more insight in hierarchical characteristics of the involved brain regions.

Before conducting the statistical analysis, we hypothesized greater involvement of the rostral subregion when performing the 2-Back condition because of higher task complexity, thus requiring more cognitive demand. Furthermore, we expected no significant difference in activation of the central subregion and decreased caudal importance with higher task complexity. Our hypothesis is supported by the results shown in the LS mean table and plot (Table 1, Figure 3) but not by the fixed effect test. These results may be explained by the negligible difference in cognitive demand between 1-Back and 2-Back. These task conditions might be insufficiently differentiating in cognitive load as these conditions might be too easy for this group of participants (healthy, young adults). This potential explanation can be confirmed because of the statistical analysis done to research the behavioral differences in different task conditions. The analysis revealed a statistically significant global difference. However, upon closer examination of the individual pairs, it was discovered that only one pair exhibited a significant difference for each behavioral measure. By virtue of the observed trend with reference to the involvement of the three lPMd subregions when task complexity increases (2-Back - 1-Back) but lacking significance in results, we could conclude that more research is necessary to assess the involvement of the lPMd subregions in different task complexities. Other N-back paradigms, with larger N-Back steps might contain significant outcomes.

In one particular study, it was demonstrated that diversity in cognitive style (i.e., individual variability of thinking, information processing and problem-solving) and encoding strategies among individuals accounted for substantial differences in task-specific functional activation across multiple brain regions, including frontal and parietal areas, during a memory task (Yeo et al., 2011). These findings could explain the absence of a significant result for our first research question.

At last, it was hypothesized that participants who show greater activation of the rostral and central region combined with a lower activation of the caudal region when task complexity increases (Figure 3), would have a higher AR and a faster RT (i.e., better task performance). Based on analysis results regarding RT, we can conclude that an overall effect of activation of the different lPMd subregions has no predictive value for RT during the N-back task. When looking more in detail at the predictive character of the different lPMd subregions involvement, we can conclude that none of the central, rostral, or caudal subregions had an influence on the RT. When we look at the results of the relationship between AR and the different subregions involvement, we noticed a low but significant predictive character because of a conflicting low RSquare value and a P-value which was smaller than the significance level. Another interpretation of our findings is that stronger rostral involvement results in better performance (i.e., AR) of a working memory task. All the other subregions (caudal and central) were not involved in the performances of the individuals during the N-back task. In the end, we wanted to prove the existence of the “rostro-cognitive effect”. The rostro-cognitive effect refers to the positive trend observed in Figure 3 where the involvement of the rostral part increases, the central part remains the same and the caudal part diminishes. As mentioned before, we hypothesized that individuals who show this rostro-cognitive effect, have better performance results (i.e., RT and AR). Based on our research we can reject this hypothesis, so individuals who show the effect illustrated in Figure 3 seem to have no better performance results during the N-back task.

Limitations

This research study has several limitations. First, no significant difference in average activation between the different lPMd subregions has been found. This could be explained by a few reasons. When looking at task complexity, the research by Li et al. (2021) has shown a difference in cognitive load when increasing the number in N-back, meaning that 0-Back condition simply demands attentional monitoring of the goal, while 2-back involves both attentional monitoring and working memory. The relatively small difference in cognitive load between 1-Back and 2-Back, could clarify the inability to find a significant difference between lPMd subdivisions. More research is necessary to understand if there is a significant difference between 1-Back and 3-, 4-, 5-Back conditions.

Second, alternative statistical approaches may potentially unravel contrasting results. For example, using multi-voxel pattern analysis (MVPA) in investigating differential activations of lPMd subdivisions during changing N-back task complexities may be of significant value in this study. MVPA techniques focus on the identification of highly reproducible spatial patterns of neural activity across experimental conditions (Mahmoudi et al., 2012) and may offer several advantages when studying activations of subdivisions within the lPMd during different levels of N-back task complexity. This section highlights the potential benefits associated with utilizing MVPA in this research context, emphasizing its ability to provide sensitivity to subtle differences, examination of individual variability, exploitation of multivariate information, generalizability, and facilitation of connectivity and network analyses. MVPA allows for a fine-grained analysis by examining activity patterns at the voxel level within the lPMd subdivisions. This high spatial resolution enables the identification of specific regions that exhibit distinct activation patterns for varying levels of N-back task complexity. Additionally, MVPA techniques present enhanced sensitivity to subtle differences in neural activity patterns, surpassing the limitations of the applied analyses in this research paper. Finally, MVPA capitalizes on the multivariate information contained in neuroimaging data. By simultaneously analyzing activity patterns across multiple voxels, MVPA surpasses the reliance on average activation levels, exposing intricate relationships and interactions between different brain regions (Mahmoudi et al., 2012).

Third, only young adults between the ages of 15 and 25 years participated in this study. When including different age categories, we could also investigate the influence of age on lPMd subdivision activation, knowing that a decrease in cognitive capabilities characterizes the aging population. The dataset consisted mostly of undergraduate and graduate students, which might not represent the heterogeneity in cognition and learning capacity found in the general population. Fourth, the results using the N-back task to evaluate working memory could be affected by attention, fatigue, strategy choice, effort, and other possible individual factors. A great deal of confounding variables could alter the outcome of the behavioral measures (AR & RT). Finally, a speed-accuracy trade-off effect could be present meaning a higher RT can implicate a sacrifice in AR.

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