Cortical contributions to cognitive control of language and beyond: evidence from functional connectivity profiles of the inferior parietal cortex and cognitive control-related resting state networks

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Cortical contributions to cognitive control of language and beyond

Evidence from functional connectivity profiles of the inferior parietal cortex and cognitive control-related resting state networks

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Blessed is He in Whose Hand is the Kingdom

Dedicated wholeheartedly to B. A. A. (AG)

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Articles in this dissertation

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Tabassi Mofrad, F., & Schiller, N. O. (2020). Cognitive demand modulates connectivity patterns of rostral inferior parietal cortex in cognitive control of language. *Cognitive Neuroscience*, *11*(4), 181–193. [Chapter 3]

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Tabassi Mofrad, F., & Schiller, N. O. (2023). Connectivity profile of middle inferior parietal cortex confirms the hypothesis about modulating cortical areas. *Neuroscience, 519*, 1-9. [Chapter 5]

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Chapter 1

General introduction

1.1 Cognitive control of language in bilinguals

Many people, as bilinguals, communicate in more than one language and, in fact, the number of bilinguals has already surpassed that of monolingual speakers in Europe and Canad (see Byers-Heinlein et al., 2019). In bilinguals, regardless of either the first language (L1) or the second language (L2) being the intended language, lexicons of both languages become activated in a parallel manner when they speak (McClelland & Rumelhart, 1981). That points to a language nonselective mechanism in bilinguals (Kroll, Bobb, & Wodniecka, 2006) which results in enhanced executive functions (Kroll et al., 2012).

Due to the simultaneous activation of languages in bilinguals (Sunderman, & Kroll, 2006), it is important to limit the activation of lexical items of the non-intended language so the interference between the languages can be kept to a minimum (Christoffels, Firk, & Schiller, 2007). The cognitive mechanism responsible for switching between languages, preventing between-language interference and communicating in the intended language is called language control or cognitive control of language (Green & Abutalebi, 2013).

Cognitive control of language is observed in language switching paradigms which are characterized by engaging and disengaging with the L1 and the L2 lexical items repeatedly. Due to cognitive control mechanisms - which necessitate reactivation of the just inhibited lexical items and suppressing the lexical items of the non-intended language - lexical production in switching contexts have longer reaction times (Philipp, Gade, & Koch, 2007; Verhoef, Roelofs, & Chwilla, 2010). In such contexts, L1 lexical items must be more suppressed when the L2 is the target language, and thus reactivation of lexical items of the L1 becomes more effortful, as explained by the *inhibitory control model* of Green (1998).

Both cortical and subcortical brain areas are involved in cognitive control of language in an adaptive manner to meet the task demands - as suggested by the *adaptive control hypothesis* (Green & Abutalebi, 2013) - in particular, in dual language and dense code-switching contexts by monitoring the language conflict, supressing the interference, and by inhibiting the non-target language.

1.2 Neural mechanisms of cognitive control of language

Various studies have investigated brain areas involved in cognitive control of language. According to Branzi et al. (2016), bilateral prefrontal cortex and bilateral inferior parietal cortex (IPC) are responsible for response selection in bilingual language control. It is emphasized that the parietal areas activate relevant responses (Bunge, et al., 2002) and the prefrontal cortex has a facilitating processing mechanism in the face of a competition between relevant and irrelevant lexical items (Miller & Cohen, 2001).

The pre-supplementary motor area, the anterior cingulate gyrus, and the left caudate are also reported to form the language control network (Abutalebi et al., 2013; Reverberi et al., 2015). It is suggested that the pre-supplementary motor area is involved in proactive switching while the involvement of the anterior cingulate gyrus in the same context is retroactive; if before the onset of a stimulus, the change in the switching context is signaled by a cue, that is proactive switching. However, in the absence of a pre-stimulus cue, any change in the switching context has to be detected by the contextual cues e.g. negative feedback; hence, that is referred to as retroactive switching (Hikosaka & Isoda, 2010). Furthermore, the anterior cingulate gyrus is involved in response selection and control, in detection of error (Hester et al., 2005; Nachev, Kennard, & Husain, 2008; Seo et al., 2019), and in influencing the intensity of the cognitive control based on the degree of language conflict (Bush, Luu, & Posner, 2000).

Regarding the left caudate, involvement in inhibiting the between-language interference is considered to be governed by this subcortical area (Abutalebi et al., 2013); besides, it is reported that the basal ganglia monitor the target language selection (Seo et al., 2019). It is worth mentioning that brain areas associated with cognitive control of language are similar to cortical/subcortical areas involved in other higher order cognitive functions (Abutalebi & Green, 2008).

With all the specifications of the functions of brain areas underlying cognitive control, yet some gaps in previous studies have not been addressed and, at times, that has resulted in contradictory research reports/lack of an accurate picture of brain areas which are believed to be involved in cognitive control.

1.3 Scope of the present study

Investigating the functional connectivity of resting-state networks related to cognitive control is more often done on neuropsychological patients than on the neurotypical participants. It is, for example, known that the patterns of resting-state functional connectivity of brain areas in the fronto-parietal network (FPN), in addition to the salience network (SN), can alleviate the harmful effects of white matter lesions on functions involving cognitive control (Benson et al., 2018). Moreover, in patients with obsessive compulsive disorder, lack of normal resting-state connectivity related to cognitive control networks is considered to result in lack of protective mechanisms against developing symptoms of that disorder (De Vries et al., 2019). However, in neurotypical bilinguals, brain intrinsic functional networks involved in cognitive control have been rarely investigated. The few studies done in this area are limited to, for instance, the influence of stronger functional connectivity between the FPN and the default mode network (DMN) on cognitive flexibility (Douw et al., 2016) and how better cognitive flexibility is indicated by stronger functional connectivity between the posterior cingulate cortex/the precuneus and other parts of the DMN (Vatansever et al., 2016).

Taking into account that the architecture of the intrinsic brain networks shapes brain connectivity profiles while engaging in a task (Cole et al., 2014) and the possibility of investigating individual differences by considering the connectivity patterns of the resting-state networks, one of the research questions in the present study is whether the individual differences in language control are reflected by the functional association of the resting state networks involved in cognitive control. To address this question, we focused on three cognitive control-related resting state networks, namely, the FPN, the DMN and the SN, and investigated how their connectivity patterns with other brain areas would characterize better cognitive control of language in Dutch-English bilinguals.

The present study also focused on the IPC in the FPN and any contribution of its tripartite organization - the rostral, the middle and the caudal clusters - to cognitive control of language. Previous studies elaborated on brain areas involved in general cognitive control functions such as the prefrontal cortex (Dixon et al., 2015; 2018), the dorsal anterior cingulate cortex (Niendam et al., 2012), and the pre-supplementary motor area (Reverberi et al., 2015). The IPC is also considered to have contributing roles to cognitive control, for instance, regarding attention (Tomasi & Volkow, 2011), memory (Martinelli et al., 2013), and language switching (Branzi et al., 2016). However, in investigating the cognitive control functions of the IPC, previous research considered this part of the cortex as a whole, regardless of the fact that each cluster of the IPC has a different transmitter receptor-based organization (Caspers et al., 2006, 2008, 2013) and thus they might have different functions from each other. Research on the white matter connectivity of the IPC along with the functional characteristics of this part of the brain also point to the IPC's cytoarchitectonically different areas (Caspers et al., 2013; Corbetta et al., 2008; Keysers & Gazzola, 2009), reflected by its tripartite organization. The resulting discrepancies in the literature, due to ignoring the parcellated structure of the IPC, are to the extent that the IPC was suggested to be a task-deactivated cortical area (Shehzad et al., 2009) and considered as part of the DMN (Doose et al., 2020; Mars et al., 2012; Raichle, 2015), which decreases its activity when our brain is focused on explicit tasks (Smallwood et al., 2021). However, in other studies, the IPC is usually known as being involved in executive functions, such as attention, memory, and processing language (Bareham et al., 2018; Buchsbaum & D'Esposito, 2011; Bzdok et al., 2016).

With such discrepancies in the literature, the other research question of the present study is whether the rostral, the middle, and the caudal IPC show connectivity patterns different from what is observed in the general behavior of the whole IPC, when cognitive control of language is concerned. Given the fact that the clusters of the IPC have different structures, we expected to observe distinct functional characteristics in each cluster, under our experimental conditions. Thus, the present study also reports the connectivity profiles of the three sub-areas of the IPC in cognitive control of language which reveal new insights in the field of neuroscience.

1.4 Methodology

The studies reported in this dissertation consist of the following workflow:

- Quick placement test
- Several picture naming experiments
- Multiband task based functional Magnetic Resonance Imaging (fMRI)
- Multiband restin state fMRI

In the next paragraphs, the specifications of the participants as well as different parts of the methodology are elaborated.

1.4.1 Participants

This study was advertised via the SONA system - volunteers can use this system to sign up for participating in research studies - as well as via posters and flyers. The following inclusion criteria were considered in recruiting participants: being right-handed, being Dutch (L1) - English (L2) bilinguals without neurological or psychiatric problems, being between 18 and 30 years old, and having normal or corrected-to-normal vision. Potential participants who expressed their interest were sent a questionnaire, and the ones that met the inclusion conditions were invited to do a quick placement test to measure their language proficiency in English. In total 52 individuals did the test. Course credits or a small financial compensation was given to motivate potential participants to take part in this research - approved by the Ethics committee of the Leiden University Medical Center (Leiden, The Netherlands).

1.4.2 Quick placement test

This test[1] has 60 multiple-choice questions, including questions of vocabulary and reading comprehension, that test takers should complete within 30 minutes. This is a paper-and-pencil test, so assessing the test takers' responses is manual. The structure of the test was clearly explained to the participants and they were supervised during the test. The English proficiency of all test takers was upper-intermediate (Mean = 44.17/60, SD = 2.23).

1.4.3 Picture naming experiments

Picture naming was used as the behavioural tool to measure participants' language switching performance, as an indication of cognitive control of language. We used IPNP (International Picture Naming Project, University of California at San Diego, USA) as well as CELEX (CEntre for LEXical information, Nijmegen, The Netherlands) lexical databases to select forty-eight pictures as the stimuli. Variables in selecting the pictures were both linguistic, such as number of letters and syllables, H statistics, initial fricative, and non-linguistic, such as visual complexity. Linguistic variables were applicable to both Dutch and English in a parallel way. That is, for instance, the name of none of the pictures started with a fricative in both languages and there was no significant statistical difference in the mean number of letters when both languages were concerned. Thus, any possibility that RT differences in Dutch and in English picture naming were influenced by the stimuli was minimized.

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[1] Oxford University Press & University of Cambridge Local Examinations Syndicate, 2001

1.4.4 Procedure

At the beginning of the picture naming experiments, which were controlled by E-Prime software[2](*Psychology Software Tools*, 2022), participants were shown all the pictures, with their names in both English and Dutch. They were also familiarized with the task by doing a short practice example and learning how the cues and the response language were associated. Then they did the experiments, using an event-related design, inside an MRI scanner and their brain activity was registered while they did different conditions of the experiments. These included naming pictures in language-switch trials and non-switch trials, in Dutch and in English.

During the switch trials - naming the pictures required switching between languages - cues indicated the target language. Cues were in the form of a red or a blue frame, preceding the stimuli by 250 ms; stimuli order was counterbalanced across participants. During the non-switch trials, naming the pictures was only in Dutch or in English. In total, the picture naming experiments included four conditions and participants named the pictures in Dutch and in English, in switch and non-switch contexts. The picture naming experiments were intended to measure participants' reaction times (behavioral data) in switching between Dutch and English languages. Bilinguals employ cognitive control mechanisms to switch to either of the two languages, and thus the reaction times in a language switching context are indications of that executive function. The behavioral data were collected four weeks after the neuroimaging session to minimize re-test effects. Participants did the same task that they did inside the MRI scanner and an SRBOX[3] (Serial Response BOX) was used to collect their RTs.

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[2] E-Prime software is developed by Psychology Software Tools, Inc.

[3] This is a button box which is used to collect responses in psychological experiments.

1.4.5 Neuroimaging methods

In this dissertation two neuroimaging techniques were used, namely, task-based fMRI and resting state fMRI, to have a clear picture of brain functional connectivity when doing the experiments and when the brain is not busy with processing external stimuli. The brain scanning methods are discussed in the following paragraphs.

1.4.5.1 Multiband task based fMRI

Via task based fMRI, the blood oxygenation level dependent (BOLD) response can be measured while participants perform a task (Huettel, Song & McCarthy, 2004). During this brain scanning method, each participant was positioned in the MRI scanner and they saw the task on an MRI safe monitor via a mirror. The task based fMRI data acquisition was synchronized with the E-prime software which was used to control the picture naming experiments. To acquire the data, in the present research, a 3 Tesla Philips Achieva TX MRI scanner which was equipped with a SENSE-32 channel head coil was used. At the beginning of the scanning sessions the high resolution anatomical images were collected followed by the functional ones. Participants were instructed to use an alarm button if for any reason they preferred to quit the experiment.

1.4.5.2 Multiband resting state fMRI

Resting state fMRI provides the possibility to investigate the connectivity between brain intrinsic networks (Seeley et al., 2007) of which the connectivity patterns of three cognitive control-related networks, namely the FPN, the SN, and the DMN were investigated in this study. During the resting state fMRI the brain is not focused on processing external stimuli. Thus, participants were instructed, while lying supine on the MRI scanner bed, to keep their eyes closed, without thinking about a particular thought or plan. They were also asked to make sure that they do not fall asleep.

1.4.6 fMRI data analyses

In the present study, detecting patterns of brain functional connectivity in both task-based and resting-state conditions was one of the main aims. To that end, psychophysiological interaction (PPI) analyses and independent components analyses (ICA) followed by dual regression were used to map the functional connectivity of the regions of interest (ROI) with other cortical/subcortical areas during task- and rest-related fMRI, respectively. Elaborations on the analyses methods are as follows:

1.4.6.1 Psychophysiological interaction (PPI) analyses

PPI analyses are used to investigate task-specific increases and decreases in the functional connectivity between brain areas (O'Reilly et al., 2012). In doing these analyses masks of the ROIs were created, using the Jülich Histological Atlas, which were binarized and thresholded at 50 percent. Masks were then projected on already pre-processed functional images. The interaction between the hemodynamic responses as the physiological variable and the time series extracted from the ROIs as the physiological variable included the psychophysiological interaction. Such interactions are in fact the functional connectivity that the ROIs have with other parts of the brain while participants performed the language switching experiments.

1.4.6.2 Independent components analyses (ICA)

These analyses were done to detect group-level independent components in resting-state networks. In the present research, a multi-session temporal concatenation, implemented in MELODIC[4] (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) was performed to carry out independent components analyses; by overlaying independent components onto the resting-state network templates, functionally and anatomically resting-state networks of interest were

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[4] MELODIC is a tool in FSL for the decomposition of fMRI data through ICA

identified. Any independent component which belonged to any other network than networks of interest, the ones outside the cortical areas, in the ventricular space and in the white matter, were not entered into the analyses.

1.4.6.3 Dual regression

To investigate any individual differences in the patterns of functional connectivity of the resting-state networks when cognitive control of language was concerned, dual regression technique was employed to do voxel-wise comparisons of the networks of interest. First group-average spatial maps were regressed into each participant's 4D dataset and then the related time series were regressed into the same 4D data. The data was thresholded at $p < 0.05$ and a threshold-free cluster enhanced (TFCE) technique was carried out to test voxel-wise differences that were statistically significant between groups, by doing 5,000 permutations.

1.5 Outline of the dissertation

This dissertation addresses brain resting state functional connectivity of the cognitive control-related networks, i.e., the FPN, the SN, and the DMN (Chapter 2) in addition to the task based connectivity profiles of the tripartite organization of the IPC (Chapter 3 to 5) in neurotypical participants.

Chapters 2 to 5 each refer to independent published research articles, discussing and concluding results in separate contexts. While in Chapter 2 by focusing on the functional connectivity patterns of three resting state networks a methodology of a different nature is elaborated on, there is an overlap in the methodology sections explained in Chapters 3 to 5 as they are devoted to brain task based functional connectivity of the rostral, the caudal, and the middle IPC, respectively.

In Chapter 2, we report the results of investigating resting state functional connectivity differences in groups with better and poor performance in cognitive control of language. We highlight that the primary somatosensory cortex has a dual function in that executive function. That is, the right primary somatosensory cortex showed functional connectivity with the IPC in the group with poorer performance in cognitive control of language. However, the left primary somatosensory cortex demonstrated increased coupling with the dorsolateral prefrontal cortex in the group with better task performance.

Chapter 3 focuses on the contribution of the rostral IPC to cognitive control of the language which is characterized with asymmetrical and lateral connectivity patterns of this part of the brain. According to our research findings, in the less demanding context of the experiments, the right rostral IPC showed more positive functional connectivity with other parts of the brain, i.e., with the cingulate gyrus, the anterior division, and the precentral gyrus, than in the more demanding context of the same experiments, which was limited to the connectivity with the cerebellum and the posterior lobe. Besides, the more demanding part of the experiments resulted in the negative functional coupling of the right rostral IPC with the postcentral gyrus, and with the precuneus cortex. Moreover, in the same experimental context, the left rostral IPC showed negative functional associations with the superior frontal gyrus and with the precuneus cortex.

Chapter 4 addresses results from mapping functional connectivity of the caudal IPC in cognitive control of language by which we proposed a brain functional category as a modulating cortical area. That is because the connectivity patterns of the caudal IPC did not demonstrate the characteristics of a cognitive control area nor the connectivity profile of parts of the cortex involved in processing general cognitive functions. At the same time, this part of the cortex showed negative functional association with the precuneus cortex which is resting-state related. That highlighted the fact that the traditional categorization of brain areas as resting-state and task-based related does not account for the connectivity profile of the caudal IPC.

In Chapter 4 we also expound that cognitive demand played a role in the number of functional connectivity of the caudal IPC with other parts of the brain but not in its left lateral functioning. The caudal IPC primarily demonstrated deactivations with other parts of the cortex in a modulating manner which were proportional to the cognitive demand. That is, the more demanding condition of our experiment resulted in more negative functional couplings of this part of the cortex with other brain areas, e.g., the precuneus cortex, the frontal pole, the cingulate gyrus, and different parts of the visual cortex.

In Chapter 5, it is delineated that the connectivity profile of the middle IPC confirms the hypothesis about modulating cortical areas. The middle IPC demonstrated very similar connectivity patterns to the caudal IPC both in terms of having mostly left lateralized functional associations, and demonstrating negative couplings with brain areas involved in cognitive control and general cognitive functions, in addition to resting state related part of the brain; the functional connectivity of the middle IPC also confirmed that the traditional categorization of brain areas does not explain the functions of modulating cortical areas.

In Chapter 6, research findings from mapping the functional connectivity of the clusters of the IPC are comprehensively presented, compared and discussed, starting with contributions of the rostral IPC to cognitive control, followed by unique connectivity profiles of the caudal and the middle IPC. The objectives are to highlight the fact that this is only the rostral IPC that contributes to cognitive control in the FPN, not the whole IPC. Besides, it is emphasized that the connectivity patterns of the middle and the caudal IPC characterize these two parietal areas with distinctive features which are dissimilar to parts of the brain involved in task performance and cortical areas related to resting state functionality of the brain.

This dissertation concludes with Chapter 7 which consists of the summary of the findings, integration of findings, limitations of the present research, suggestions for future research, and the conclusion.

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Chapter 2

Dual function of primary somatosensory cortex in cognitive control of language: evidence from resting state fMRI

This chapter is based on:

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Abstract

Resting state functional connectivity can be leveraged to investigate bilingual individual differences in cognitive control of language; however, thus far no report is provided on how the connectivity profiles of brain functional networks at rest point to different language control behavior in bilinguals. In order to address this gap in state-of-the-art research we did a functional connectivity analysis on the resting state data acquired via multiband EPI to investigate three resting state networks of interest namely, the frontoparietal network, the salience network, and the default mode network, which are related to cognitive control, between two groups of Dutch-English bilinguals based on how they performed in a language switching task. Results demonstrated that there is the increased coupling of the left primary somatosensory cortex with the dorsolateral prefrontal cortex in the group with better performance in cognitive control of language and the increased coupling of the right primary somatosensory cortex with the inferior parietal cortex in the group with poorer performance in this executive function. As regards these results, we claim that the primary somatosensory cortex has a dual function in coupling with the dorsolateral prefrontal cortex and the inferior parietal cortex in the frontoparietal network, and in fact, in what characterizes bilingual individual differences in cognitive control of language in healthy participants. The results of this study provide a model for future research in cognitive control of language and may serve as a reference in clinical neuroscience when bilinguals are diagnosed with dysfunction in cognitive control.

2.1 Introduction

Resting state functional connectivity MRI provides the means to investigate brain intrinsic functional networks, by detecting similar patterns of functional activity shared between separated brain regions, when the brain is not processing external stimuli (Fox & Raichle, 2007). Among different brain intrinsic functional networks, three networks are recognized to be involved in cognitive control, of which language control is one component. One of these networks is the frontoparietal network (FPN) which includes the anterior prefrontal, the dorsolateral prefrontal, the dorsomedial superior frontal/anterior cingulate, the inferior parietal lobule, and the anterior insular cortex (Vincent et al., 2008). By controlling the involvement of other brain networks, this network plays an important role in meeting task demands involved in cognitive control (Cole et al., 2013; Spreng et al., 2013).

The other network related to cognitive control is the salience network (SN) which includes the anterior insula/inferior frontal area, the dorsal anterior cingulate and the supramarginal gyri (Seeley et al., 2007). This network is also a task-related network which is active in different aspects of cognitive control, for instance working memory and task switching (Luks et al., 2002; Owen et al., 2005, Dosenbach et al., 2007). The third network related to cognitive control is the default mode network (DMN) which includes the medial parietal (the precuneus and the posterior cingulate), the bilateral inferior parietal and the ventromedial frontal cortex (Smith et al., 2009). The DMN mostly modulates cognitive control by reducing its amount of activity when performing a task and the strength of functional connectivity within its nodes (Dang et al., 2013). This network is recognized as the posterior and the anterior DMNs (Laird et al., 2017).

Investigating brain functional connectivity in healthy participants with regard to the above-mentioned networks related to cognitive control has not been widely reported in the literature and among the few reported ones (Douw et al., 2016; Vatansever et al., 2016), no report is provided on how the functional connectivity of the FPN, the SN and the DMN at rest is responsible for bilingual individual differences in language control. This is in fact what we have addressed in this study by focusing on cognitive control of language which prevents production of words from an unintended language, when bilinguals speak in the target language (Abutalebi & Green, 2007; Green & Abutalebi, 2013). Such cognitive mechanisms which engage brain areas involved in cognitive control (Abutalebi & Green, 2007; Branzi et al., 2016) are characterized with switching to another language or rather language engagement and stopping to speak in the other language, recognized as language disengagement (Abutalebi & Green, 2008; Kroll et al., 2006).

In a few studies, the brain functional connectivity with respect to cognitive control has been investigated. This issue has partly been addressed by Douw et al. (2016), by investigating how the state-dependent variability of the dynamic functional connectivity (vdFC) is related to cognitive flexibility. They studied the brain functional connectivity during both the resting state and the task-based functional magnetic resonance imaging, using a block design Stroop task. According to this research, the state-dependent vdFC between the FPN and the DMN is related to cognitive flexibility, and that better performance in this executive function is characterized with a more dynamic connectivity between the FPN and the DMN when participants performed a cognitive flexibility task; however, the reverse association of the FPN–DMN vdFC was true in the resting state. In another study, Vatansever et al. (2016) conducted an experiment by using an intra/extradimensional set-shifting task (IED) outside the scanner to investigate a link between DMN connectivity and cognitive flexibility as an index of cognitive control. Associating fewer errors in doing different parts of the IED task with more of this executive function, they reported that stronger posterior cingulate cortex/precuneus functional association with the rest of the default mode region is indicative of more cognitive flexibility.

Considering a previously stated hypothesis that the language control behavior in bilinguals characterizes the brain connectivity profiles in cognitive control regions in bilinguals (Luk et al., 2011), Grady et al. (2015) by reporting stronger intrinsic functional associations in FPN and DMN in bilinguals also emphasized the role of these two networks in relation to cognitive control. Moreover, in some other studies, the interactions between DMN, the parahippocampal gyri, the angular gyri (Spreng et al., 2009) and FPN including inferior parietal regions, inferior frontal and dorsolateral regions (Spreng et al., 2013) in different aspects of cognitive control are reported.

With respect to studies on brain functional connectivity patterns, brain regions that fluctuate together to do a particular task, also work together during the resting state functional connectivity (Smith et al., 2009, Cole et al., 2014). Therefore, there is a high similarity between brain regions involved in the resting state and the task-related functional connectivity (Fair et al., 2007). Based on an assumption that an intrinsic functional connectivity architecture, characterized by the resting state functional connectivity, is present across brain regions (Fox & Raichle, 2007, Vincent et al., 2007) Cole et al. (2014) reported that the brain connectivity architecture related to doing a task is shaped by the architecture of the brain intrinsic networks and thus, between these two there is a strong association. These reports have also provided the bases for more research regarding individual differences in the resting state functional connectivity.

In previous studies the involvement of three resting state networks, namely the FPN, the SN, and the DMN in cognitive control has been pointed out, however, no elaborations have been provided on how these networks contribute to individual differences in different aspects of cognitive control. Moreover, as it is emphasized that brain's connectivity profiles in doing a task are formed by the resting state networks, this would provide the rationale to investigate how the intrinsic networks signal individual differences in the first place. Thus, focusing on our research question whether the individual differences in language control are reflected by the functional association of the resting state networks involved in cognitive control, we addressed the above-mentioned gap in previous studies, using a multiband EPI technique.

2.2 Experimental procedures

2.2.1 Participants

In this study fifty-two healthy (11 males and 41 females), right-handed psychology students at Leiden University took part. They had normal or corrected-to-normal vision and they were 18–27 years old. These participants were all sequential Dutch–English bilinguals, born to native Dutch parents. In order to measure the English language proficiency of the potential participants we used the quick placement test (University of Cambridge Local Examinations Syndicate 2001). We later excluded four participants from this study because they had excessive movements when we were doing resting state data acquisition.

When we recruited participants we excluded left-handed volunteers as they process language in a different way from right-handed people, and anyone who had any report and history of neurological or psychiatric problems. We asked final participants for their written informed consent before they could take part in the experiment and we compensated for their participation by giving them course credit or paying them a small amount of money. The medical ethics committee of Leiden University Medical Center (LUMC) (Leiden, the Netherlands) approved the protocol of this experiment.

2.2.2 Stimuli

From the International Picture Naming Project (IPNP – https://crl.ucsd.edu/experiments/ipnp/) we selected forty-eight pictures and in doing so we took into account the following variables in both English and Dutch languages (see Table 2.1 for a summary): RT (mean), number of letters and syllables, H statistics which points to the rate of response agreement by participants when they name a picture, word complexity (we did not use any compound words as they increase RT) and initial fricative which specifies if a word begins with a consonant sound such as f or v because such words are associated with having longer naming latencies (see Bates et al., 2003).

Table 2.1

Summary of matching the variables of the stimuli. This summary provides details on each variable that the stimuli were matched on in L1 & L2 with t*-test statistics*

Name of variable*	Mean L1	Mean L2	SD L1	SD L2	t	P Value
Number of letters	4.71	4.67	1.43	1.21	0.154	0.878
Number of syllables	1.3	1.33	0.46	0.52	-0.42	0.678
RT (mean)	885.51	849.04	93.81	102.39	1.82	0.072
H statistics	0.23	0.22	1.86	3.28	1.33	0.894
Initial fricative	0.1	0.06	0.31	0.245	7.33	0.465
Word complexity	0.00	0.00	0.00	0.00	**	**

Note. *For a detailed description on the identification of variables see: https://crl.ucsd.edu/experiments/ipnp/method/getdata/uspnovariables.html
**These values could not be computed because the standard deviations of both groups are 0. In fact, no complex words were used.

In this study we used both the database provided by IPNP and the CELEX lexical database as references for the variables and we created two sets of twenty-four stimuli which were counterbalanced across participants (set A and set B). These two sets were parallel with respect to the above-mentioned variables along with, visual complexity, word frequency and conceptual complexity. As the visual complexity which refers to the level of details in an image, and conceptual complexity which points to how many animals, objects and persons are shown in each image (Snodgrass & Vanderwart, 1980) are language-independent and in fact are features of images, we did not match these variables on L1 and L2, however, we matched these two variables on the two sets of twenty-four stimuli.

2.2.3 Language switching task

In this study we used a language switching task which is indicative of language control and we used E-Prime software to control this task. We presented the stimuli in the center of the screen and we asked participants to name them as quickly as possible following a cue which indicated in which language – Dutch (L1) or in English (L2) – the stimuli should be named. This experiment included two types of trials in four conditions, i.e. there were switch trials in which the cued language was different from the preceding trial (i.e. from Dutch to English or from English to Dutch) and non-switch trials in which the language remained the same as in the previous trial. At the beginning of each trial we showed a visual cue in the form of a red or blue frame for 250 ms and this was counterbalanced across participants. This visual cue also preceded a picture and instructed participants to name the upcoming picture either in Dutch or in English. The cue was then followed by a fixation cross for 500 ms and presentation of a picture for 2010 ms. The end of each trial was marked by presentation of a jittered blank screen which varied between 690 and 2760 ms. We used Optseq program in order to pseudo-randomize the order of stimuli and to determine the length of each intertrial blank screen interval.

Before acquiring the fMRI data, participants practiced the behavioral part of the experiment. That included (a) making participant familiarized with the pictures that we used in the experiment. In this section participants saw all the pictures with their Dutch and English names; (b) making participants familiarized with the association of the visual colored cue and the related language and the task procedure. In this section participants did a short scale of the task that was similar to the main task without using the target pictures. We collected participants' responses by using a voice key outside the MRI scanner.

2.2.4 Resting state fMRI acquisition

All resting state data were acquired on a 3 Tesla Philips Achieva TX MRI scanner at the Leiden University Medical Center, equipped with a SENSE-

32 channel head coil. Prior to resting state functional images, high-resolution anatomical images were collected for co-registration with the functional ones. These included a 3D gradient-echo T1-weighted sequence with the following parameters: TR= 7.9 ms, TE = 3.5 ms, FA = 8°, FOV = 250 x 195.83 x 170.5, 155 slices 1.1×1.1×1.1 mm3. During the resting state fMRI acquisition, 700 T2*-weighted whole brain multiband EPIs were acquired, excluding 6 dummy scans preceding the dynamic ones. The scanning parameters in the resting state fMRI acquisition are as follows: TR = 690 ms, TE = 30 ms, multiband factor = 4, FA = 55°, FOV = 220 x 220 x 121, 44 slices 2.75 × 2.75 × 2.75 mm.

2.3 Data analysis

2.3.1 Behavioral data analysis

We processed participants' reaction times (RTs) in doing the language switching task in switch and non-switch trials by using SPSS software version 23. We used a two (language: Dutch vs. English) by two (context: switch vs. non-switch) repeated-measures ANOVA and we looked into any main effects of the factors and any possible interactions. In addition, we ran subsequent paired *t*-tests to see if the language switching task produced statistically significant switch costs (RT switch – RT non-switch) in both L1 (Dutch) and L2 (English). In the following, we divided participants into two groups to investigate if individual differences in language control are influenced by the functional connectivity of the resting state networks involved in cognitive control.

We measured language control with regard to participants' L1 and L2 switch costs. We averaged the switch costs across L1 and L2, separately. Participants with switch costs less than the mean value in both L1 and L2 conditions were categorized as having better performance in the language switching task (indicating better language control) compared with the ones with switch costs more than the mean value in both L1 and L2 (indicating poorer language control). To make sure that these two groups were statistically different from each other, we used a one-way MANOVA (group with switch costs less than the mean value in both L1 and L2 vs.

group with switch costs more than the mean value in both L1 and L2) and a significance threshold of $p < 0.05$.

2.3.2 Pre-processing of resting state images

Resting state images were processed using FSL software Version 5.0.10 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.15, was used for pre-processing. The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). The functional images were registered to MNI-152 standard space (T1-standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) using a three-step registration from functional to high-resolution images, which were registered to T1-weighted structural images, and then registered to the standard space of the MNI template. Registration was carried out using FLIRT (Jenkinson and Smith, 2001, Jenkinson et al., 2002).

2.3.3 Functional connectivity analyses

Multi-session temporal concatenation with 70 independent components (high dimensional ICA) and variance normalization was used to carry out group ICA as implemented in MELODIC Version 3.15, using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) Version 5.010. Multi-session temporal concatenation performs a single ICA run on the concatenated data matrix to estimate group-level independent components in RSNs. Ten ICs were identified as anatomically and functionally classical RSNs of interest. We overlaid IC maps onto previously defined resting-state network templates (Smith et al., 2009;

Laird et al., 2011) and we selected IC maps with the highest overlap for subsequent analyses. The rest of the ICs belonging to other networks or with majority of voxels in white matter, ventricular space, and outside of the brain were discarded.

The analysis for the individual differences in language control between groups was carried out using FSL dual regression technique that provides voxel-wise comparisons of the resting-state fMRI (Littow et al., 2010). First, for each participant, the group-average set of spatial maps was regressed (as spatial regressors in a multiple regression) into the participant's 4D space-time dataset. This resulted in a set of participant-specific time series, one per group-level spatial map. Next, those time series were regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of participant-specific spatial maps, one per group-level spatial map (Filippini et al., 2009). We performed dual regression analysis with variance normalization. In order to correct data thresholded for $p < 0.05$ (Nichols & Holmes, 2002) and to test statistically significant voxel-wise differences between groups via threshold-free cluster enhancement(TFCE), and to correct for multiple comparisons across IC maps, the FSL randomize tool with 5,000 permutations (Filippini, et al., 2009) was used. In accordance with Reineberg et al. (2015), the permutation testing procedure was done for each set of participant-specific RSNs (one for each group-level RSN of interest).

2.4 Results

2.4.1 Behavioral data

Data from 48 healthy volunteers were analyzed (see Table 2.2). Repeated-measures ANOVA showed main effects for both context (switch & non-switch) $F_{1,47} = 76.3$, $p < 0.0001$ and language (L1 & L2) $F_{1,47} = 49.9$, $p < 0.0001$ with no interaction between these two factors $F_{1,47} = 3.1$, $p < 0.085$, indicating symmetrical switch costs and that the language switching task produced significant switch costs (RT switch – RT non-switch) in both L1 (Dutch) $t_{47} = 5.8$, $p < 0.0001$, and in L2 (English) $t_{47} = 8.7$, $p < 0.0001$.

Table 2.2
Summary of the behavioral data

Switching context	Mean RT (ms)	SD
Switch trials		
L1 to L2	764.14	112.88
L2 to L1	794.15	126.64
Non-Switch trials		
L1 to L1	747.22	110.68
L2 to L2	701.87	99.87
Switch cost in L1 condition	46.93	55.85
Switch cost in L2 condition	62.27	49.51

Note. The behavioral data regards the reaction time (RT) in performing language switching task in both L1 and L2.

Because there is no interaction between the factors language and context, there is no possibility that the difference in participants' reaction times (RTs) between non-switch trials and switch trials in either the weaker language (English/L2) or the stronger language (Dutch/L1) is influenced differently by the context. Furthermore, since we had matched RT (mean), H statistics, the number of letters and syllables, initial fricative, word frequency and morphological complexity across stimuli in L1 and L2, it is not possible that because of more difficult or easier stimuli, naming a picture in one language might have benefited or suffered more than naming a picture in the other language.

According to Table 2.2, in this language switching task L1 is slower than L2 in both switch and non-switch trials. Previous studies also reported such behavioral results (Christoffels et al. 2007; Costa & Santesteban, 2004; Gollan & Ferreira, 2009; Verhoef et al., 2009) and this is probably as a result of suppressing the stronger language more in a language switching context - which makes its retrieval also more effortful - in order for the bilinguals to speak in the weaker language (for more details, see Green, 1998).

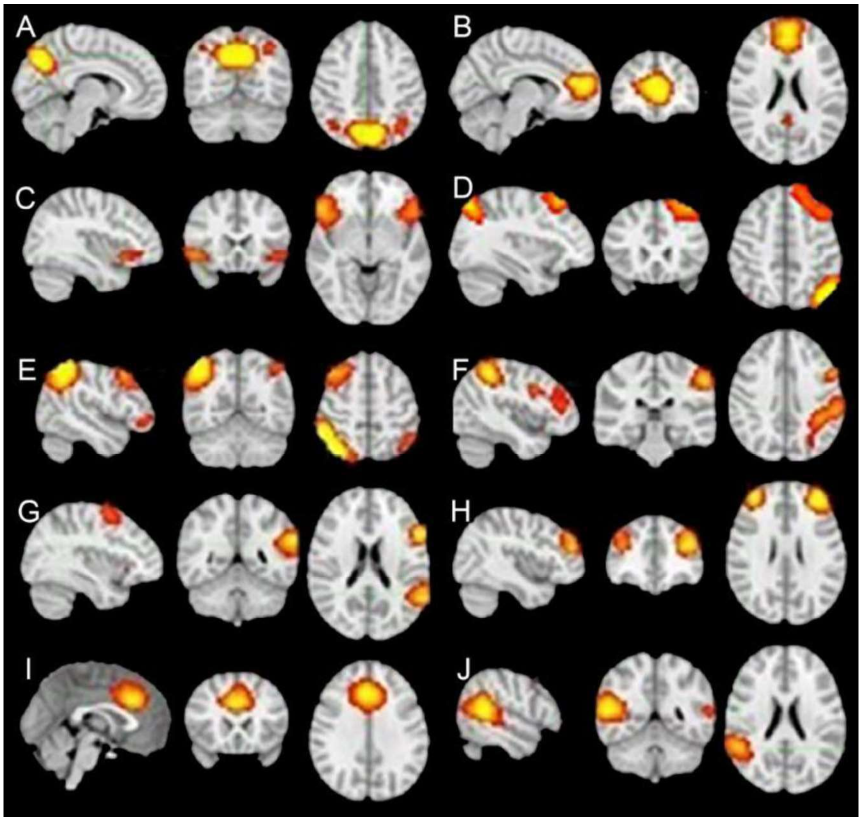
In order to investigate how individual differences in cognitive control of language are influenced by the functional connectivity of the resting state networks involved in cognitive control we averaged the switch costs across L1 and across L2, separately. Participants with switch costs less than the mean value in both L1 and L2 conditions were categorized as having better performance in the language switching task, indicating better language control (mean age 20.25), and participants with switch costs more than the mean value in both L1 and L2 were categorized as having poorer performance in this task, indicating poorer language control (mean age 22.17). Processing the data based on grouping participants via a one-way MANOVA (group with switch costs less than the mean value in both L1 and L2 vs. group with switch costs more than the mean value in both L1 and L2) showed that there was a statistically significant difference between these two groups ($F_{2, 21} = 29.97$, $p < 0.0001$; Wilks' Lambda = 0.26; partial eta squared = 0.74); in addition, considering the results for the dependent variables separately, a Bonferroni-adjusted alpha level of 0.025 showed that in both L1 switch cost ($F_{1, 22} = 54.06$, $p < 0.0001$, partial eta squared = 0.71) and L2 switch cost ($F_{1, 22} = 33.26$, $p < 0.0001$, partial eta squared = 0.6) these two groups were also statistically different.

2.4.2 Independent components analysis

Ten RSN related IC maps of interest, namely, the DMN, the SN, and the FPN were identified in all participants (see Fig. 2.1). To identify these maps we overlaid the IC maps onto the previously defined resting state network templates (Smith et al., 2009; Laird et al., 2011) and we selected the IC maps with the highest overlap for subsequent analyses using fslcc. The rest of the ICs with majority of voxels in the white matter, in the ventricular space, and outside of the brain were discarded.

Figure 2.1

Resting state networks from the current study (5 < z < 12)



Note. Location (Z-COG) of the resting state networks: (A) IC 14 (8, −64, 44), (B) IC 18 (8, 46, 22), (C) IC 30 (37, 20, −6), (D) IC 1 (−35, 25, 48), (E) IC 5 (48, −57, 55), (F) IC 8 (−42, −30, 39), (G) IC 13 (−37, −50, 21), (H) IC 35 (42, 38, 26), (I) IC 42 (−1, 23, 32), (J) IC 63 (54, −49, 23). In this figure, the right side of the brain is on the left side of the images.

According to Laird et al. (2017), the FPN is composed of many constituent sub-networks by having high level of fractionation on the right side and medium level of fractionation on the left side, due to inter-lobal communication within this network. In this study, we also report such fractionation and sub-networks in the FPN - which includes the anterior prefrontal, the dorsolateral prefrontal, the dorsomedial superior frontal/anterior cingulate, the inferior parietal lobule, and the anterior insular cortex (Vincent et al., 2008) - with respect to IC 1 (the left inferior parietal lobule, and the superior frontal gyrus), IC 5 (mostly covering the right part of the FPN), IC 8 (the middle frontal gyrus, and the left inferior parietal lobule), IC 13 (the inferior frontal gyrus, the middle frontal gyrus, and the left inferior parietal lobule), IC 35 (the dorsolateral prefrontal cortex), IC 42 (the cingulate gyrus, anterior division), IC 63 (the inferior parietal lobule). We also report the DMN in terms of the anterior DMN (IC 18) and the posterior DMN (IC 14). IC 30 pertains to the SN.

2.4.3 Dual regression

We investigated between-group differences in the voxel-wise spatial distribution of the functional connectivity maps on ten ICs. Between-group differences were revealed in two ICs, namely, IC 35 and IC 63 due to their different functional connectivity between groups. In group with better performance in language task switching, there was increased coupling of the left primary somatosensory cortex (BA1) with IC 35, a subcomponent of the FPN including dorsolateral prefrontal cortex (DLPC).

Table 2.3

Dual regression summary

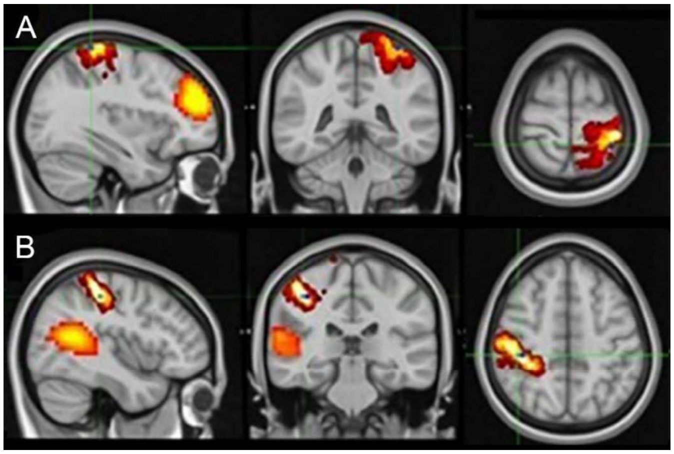
Network	IC	Voxels	Coordinates	*P* value (corrected)
Subcomponent of FPN (dorsolateral prefrontal cortex)	35	3569	-34,-42,68	0.0134
Subcomponent of FPN (Inferior parietal cortex)	63	5751	42,-30,48	0.0176

Note. This summary provides further specifications about IC 35 (DLPC) and IC 63 (inferior parietal cortex) that characterize between group differences with regard to the shape of these two ICs.

In group with poorer performance in the language switching, there was increased coupling of the right primary somatosensory cortex (BA2) with IC 63, a subcomponent of the FPN including the inferior parietal cortex (see Fig. 2.2 and Table 2.3).

Figure 2.2

Results of the dual regression analyses



Note. These results reveal between-group differences in the shape of IC 35 (DLPC) and IC 63 (inferior parietal cortex). In panel A between-group difference – group with better performance in language control > group with poor performance in language control – is overlaid on (left) BA1 and then overlaid on IC 35. In panel B between-group difference – group with poor performance in language control > group with better performance in language control – is overlaid on (right) BA2 and then overlaid on IC 63.

2.5 Discussion

In this study, we investigated how individual differences in language control are influenced by the functional connectivity of the resting state networks involved in cognitive control, given the fact that brain regions that fluctuate together to do a particular task, also work together during the resting state functional connectivity (Cole et al., 2014; Smith et al., 2009). Moreover, the intrinsic network architecture which is present across brain regions has strong associations with brain's functional networks involved in performing a task (Fox & Raichle, 2007; Vincent et al., 2007). We benefitted from the multiband EPI in which the sensitivity of BOLD acquisitions (Kundu et al., 2012), the spatial and/or temporal resolution (Chen et al., 2015) and the sensitivity of detecting brain functional connectivity (Liao et al., 2013; Preibisch et al., 2015) are increased.

For our research purpose, we used a language switching task outside the scanner room, in which language engagement and disengagement, e.g. switching to L1 and switching to L2 is a key factor. We divided the participants into two groups based on their L1 and L2 switch costs. Better language control is characterized with better performance in language switching task and poorer language control is associated with higher switch costs in this task. In this study, we focused on three resting state networks of interest namely the FPN, the SN and the DMN as the networks which are related to cognitive control (Seeley et al., 2007; Smith et al., 2009; Vincent et al., 2008). Language control engages areas involved in cognitive control, and also similar mechanisms are reported to be at work in both language control and cognitive control (Abutalebi & Green, 2007; Branzi et al., 2016).

Regarding the relation of the resting-state networks of interest in the current research with functions which require cognitive control, the FPN has an important role in meeting task demands involved in cognitive control (Cole et al., 2013; Spreng et al., 2013) and the SN has repeatedly been reported to be active in different aspects of cognitive control, such as working memory and task switching (Dosenbach et al., 2007; Luks et al., 2002; Owen et al., 2005). Besides, the DMN modulates cognitive control by reducing the strength of the functional connectivity within nodes of this network when the brain is busy with different functions requiring cognitive control (Dang et al., 2013). In total, we detected ten ICs maps of interest related to the FPN, the SN and the DMN and we carried out FSL dual regression technique that provides voxel-wise comparisons of the resting state fMRI (Littow et al., 2010) to investigate the association between better and poorer language control with the patterns of the functional connectivity of the resting state networks of interest.

In our study, we observed the increased coupling of the left primary somatosensory cortex (BA1) with IC 35, a subcomponent of the FPN including DLPC in the group with better performance in the language switching task. Moreover, we detected the increased coupling of the right primary somatosensory cortex (BA2) with IC 63, a subcomponent of the FPN including the inferior parietal cortex in the group with poorer performance in this task.

Investigating the brain resting state functional connectivity related to the functions requiring cognitive control in healthy participants has not been widely reported in the literature and among the few reported studies we found the one by Reineberg et al. (2015) more relevant to our study. They investigated how resting state networks reveal individual differences in both common and specific aspects of cognitive control such as response inhibition, task set shifting and working memory updating. Based on this study, it is reported that individuals with better task performance involving cognitive control may have more expanded resting state networks, with regard to the FPN. In fact, having better performance in functions that require cognitive control is characterized with the FPN being more extended due to the connectivity with the nodes in particular with somatosensory regions (Tabassi Mofrad & Schiller, 2019). The FPN has an important role in meeting task demands involved in cognitive control (Cole et al., 2013; Spreng et al., 2013); thus, better task performance in functions requiring cognitive control is directly reflected by the patterns of the functional connectivity of this network at rest. This is of course in accordance with the previously stated idea that the intrinsic network architecture which is present across brain regions has strong associations with the brain's functional network involved in performing a task (Fox & Raichle, 2007; Vincent et al., 2007).

Results from the current research with respect to the functional connectivity of the FPN in the groups with better and poorer performance in language switching task to some extent replicate the results from Reineberg et al. (2015). Better performance in the language switching task, indicative of better language control, is associated with the coupling of the FPN with the somatosensory cortex at rest, and the somatosensory regions are involved in stimulus-response mappings when performing a task. Therefore, the increased coupling of the FPN at rest with the regions involved in stimulus-response mapping in individuals with better performance in the language switching task is indicative of better linking the stimuli and the response when doing the task. However, what the current study adds to the previous literature is that connectivity patters of the left somatosensory cortex, but not the right side of this part of the cortex is associated with better task performance in language switching. In fact, we demonstrated that the primary somatosensory cortex has a dual function in coupling with the FPN. We further elaborated that the (left) BA1 and the (right) BA2 couple with different parts of this network, the DLPFC and the IPC, respectively, to characterize individual differences in cognitive control of language. That is, the increased coupling of the left primary somatosensory cortex (BA1) with the DLPC is associated with better language control and the increased coupling of the right primary somatosensory cortex (BA2) with the IPC is linked with poorer language control in healthy bilingual participants.

With regard to studies on human motor cortex, it is emphasized that this part of the brain plays an important role in mental rotation (Cona et al., 2017; Tomasino et al., 2005), and in fact it is the left side of the motor cortex that controls mental rotation in right-handed individuals (Tomasino et al., 2005). As somatosensory cortex converges to the motor cortex circuitry (for a review see Hooks, 2017), and in our study only right-handed volunteers participated, so the left somatosensory cortex appears to be linked to cognitive control or language switching, as if one is manually switching between languages. Thus, it seems that participants, with better performance in language switching task, use the left motor cortex circuitry in a network fashion to switch between languages; However, the involvement of the right sensorimotor cortex in participants with poorer performance in language task switching is indicative of less efficiently connected regions involved in motor cortex circuitry.

Regarding the parietal regions as well as DLPFC, which are parts of the FPN, the activities of these parts of the cortex in some functions requiring cognitive control, in particular in task switching have already been reported in the literature (Collette et al., 2005; Derrfuss et al., 2005; Esterman et al., 2009; Tabassi Mofrad & Schiller, 2019; Tabassi Mofrad & Schiller, 2020; Wager et al., 2004). Based on our research results, we suggest that BA1 and BA2 in the right and left part of this cortex, with regard to their patterns of the functional connectivity with the FPN at rest, seem to have other secondary connectivity outside of the control network. However, further research is needed to investigate how the primary somatosensory cortex adopts different functions in BA1 and BA2 in the right and left part of this brain area, in particular, with regard to the stimulus-response mapping as coupling these regions within the somatosensory cortex with the DLPFC and the IPC, in our study, has characterized better and poorer language control in individuals.

In this study, by dividing participants into two groups, we investigated whether individual differences in language control are influenced by the functional connectivity of the resting state networks involved in cognitive control, but we could not match these two groups with regard to their IQ as this variable was not part of the including criteria in participant recruitment. We suggest that in future research participants' IQ be also considered as an including criteria to see how this might influence task takers language control behavior. Besides, in this study we did not have access to MRI compatible microphone, thus participants did the language switching task also outside the scanner. This would count as a limitation in our study.

As mentioned earlier in this discussion, in language control - marked with language engagement and disengagement (Abutalebi & Green, 2008; Kroll et al., 2006) - and in cognitive control similar brain areas are at work (Abutalebi & Green, 2007; Branzi et al., 2016). Therefore, the results of this study will have broader implications especially for clinical neuroscience in bilingual populations. Autism spectrum disorder, attention deficit hyperactivity disorder, and obsessive-compulsive disorder are all characterized by dysfunction in cognitive control (Corbett et al., 2009; Sergeant et al., 2002; Willcutt et al., 2005; Zandt et al., 2009). However, research into the neurobiology of cognitive control deficits is not well reported in the literature. By addressing what characterizes individual differences in cognitive control of language in healthy bilingual participants in terms of the functional connectivity of the brain networks related to cognitive control at rest, the current study provides a possible model for future research and may serve as a reference in clinical neuroscience when bilinguals are diagnosed with the above-mentioned disorders.

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Chapter 3

Cognitive demand modulates connectivity patterns of rostral inferior parietal cortex in cognitive control of language

This chapter is based on:

Tabassi Mofrad, F., & Schiller, N. O. (2020). Cognitive demand modulates connectivity patterns of rostral inferior parietal cortex in cognitive control of language. *Cognitive Neuroscience*, *11*(4), 181–193.

Abstract

The inferior parietal cortex (IPC) is involved in different cognitive functions including language. In line with the correlated transmitter receptor-based organization of the IPC, this part of the brain is parcellated into the rostral, the middle and the caudal clusters; however, the tripartite organization of the IPC has not been addressed in studies with a focus on cognitive control of language. Using multiband EPI, in this study we investigated how the rostral IPC contributes to this executive function in bilinguals. In doing so, we focused on the functional connectivity patterns of this part of the cortex with other brain areas in a context characterized with language engagement and disengagement that recruits the neural mechanisms of cognitive control. We found that in switching to L2, which was cognitively less demanding, the right rostral IPC had positive functional connectivity with the anterior division of the cingulate gyrus and the precentral gyrus. However, in switching to L1, which was cognitively more demanding, the right IPC rostral cluster had negative functional coupling with the postcentral gyrus and the precuneus cortex and positive connectivity with the posterior lobe of the cerebellum. In this condition, the left IPC rostral cluster had negative functional coupling with the superior frontal gyrus and the precuneus cortex. Thus, the connectivity patterns of the rostral IPC was influenced by the cognitive demand in an asymmetrical and lateral manner during cognitive control of language.

3.1 Introduction

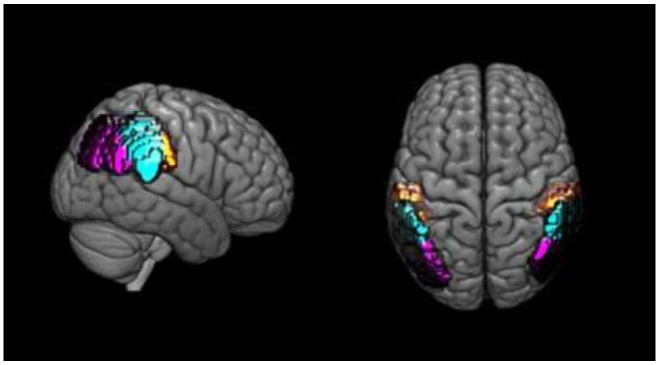
Cognitive control of language refers to the cognitive mechanisms that enable bilinguals to avoid interference from a non-target language when they utter a word in an intended language (Abutalebi & Green, 2007; Green & Abutalebi, 2013). Engaging brain areas involved in general aspects of cognitive control (Abutalebi & Green, 2007; Branzi, Della Rosa, Canini, Costa, & Abutalebi, 2016), cognitive control of language is characterized with language engagement and disengagement, to switch to another language and to stop speaking in one language accordingly (Abutalebi & Green, 2008; Kroll, Bobb, & Wodniecka, 2006). With regard to cognitive control of language, the inferior parietal cortex (IPC) is associated with a response selection system and its function is dependent upon the amount of inhibition which is needed, e.g., to avoid L1 (first language) lexical items when L2 (second language) lexical items are produced (Branzi et al., 2016). Such a function of the IPC in language task switching paradigms is mostly highlighted with regard to updating, shifting and inhibition, in particular (Abutalebi & Green, 2008; Price, Green, & von Studnitz, 1999; Sohn et al., 2000; Wager, Jonides, & Reading, 2004).

Thus far, only as a whole and irrespective of its tripartite organization, the IPC has been addressed either with regard to cognitive functions in broader terms - e.g., attention (Corbetta, Patel, & Shulman, 2008; Tomasi & Volkow, 2011), action-related functions (Caspers, Zilles, Laird, & Eickhoff, 2010; Keysers & Gazzola, 2009), self-perception (Ionta et al., 2011), memory (Martinelli, Sperduti, & Piolino, 2013), and social cognition (Molenberghs, Johnson, Henry, & Mattingley, 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014) - or with a focus on cognitive control of language (Abutalebi & Green, 2007, 2008; Branzi et al., 2016).

With respect to structural parcellation of the human IPC, seven cytoarchitectonical areas are defined in this brain region, namely, PFt, PFop, PF, PFm, PFcm, PGa, and PGp, suggestive of functional differentiation in the IPC (Caspers et al., 2006, 2008). Based on the idea that characteristics of these cytoarchitectonically segregated brain regions should be reflected by receptor architectonics, Caspers et al. (2013) measured the density of fifteen different receptors in each part of the IPC and reported that with regard to a correlated transmitter receptor-based organization, this brain region consists of three clusters, that is, a rostral cluster covering areas PFop, PFt, PFcm, a middle cluster covering areas PF and PFm, and a caudal cluster covering areas PGa and PGp. Ruschel et al. (2014), in addition, via diffusion-weighted magnetic resonance imaging combined with probabilistic tractography, investigated the connectivity patterns of the human IPC, in order to parcellate this brain region. In line with parcellation of the IPC into rostral, middle and caudal clusters, based on a correlated transmitter receptor-based organization (Caspers et al., 2013), they also reported three subareas in the IPC akin to the above-mentioned clusters (see Figure 3.1).

Figure 3.1

Lateral right and dorsal view of the IPC division to the rostral (yellow-red), the middle (cyan), and the caudal (violet) clusters



The white matter connectivity as well as functional properties of the IPC is reported to be reflected by its structural division into cytoarchitectonically different areas (Caspers et al., 2013; Corbetta et al., 2008; Keysers & Gazzola, 2009). According to Caspers et al. (2011), the fiber tracks between subareas of the IPC and other brain areas do not show the same characteristics; while the caudal IPC has strong connections with the posterior parietal, the higher visual and temporal areas, the rostral IPC is more connected with the inferior frontal, motor, premotor, and somatosensory areas. The connectivity patterns of the middle IPC, however, show similarities with those of both caudal and rostral IPC, with major connections with the frontal, superior parietal, and intraparietal areas. In addition, some other earlier studies using Diffusion Tensor Imaging (DTI) had already pointed to such tripartition of the cortex in the IPC (Rushworth, Behrens, & Johansen-Berg, 2006; Tomassini et al., 2007).

Functional properties of the IPC confirm the tripartition of this part of the cortex. Shalom and Poeppel (2008) proposed that different aspects of language are processed in each of the three subareas of the IPC. According to this study, the caudal IPC areas process semantic content of words or sentences, while the rostral IPC areas are involved in sound and single phoneme processing. The middle IPC areas, in addition, process the underlying rules to assemble basic language components. The tripartite organization of IPC with respect to the functional properties of this part of cortex is not limited to language-related tasks; with regard to some other earlier studies, the middle IPC areas are involved in processing spatial or non-spatial attention tasks (Boorman, Behrens, Woolrich, & Rushworth, 2009; Caspers et al., 2011; Corbetta et al., 2008), and the caudal IPC areas are activated during moral decision making (for a review see Raine & Yang, 2006). The rostral IPC, however, seems to contribute to storing abstract somatosensory information (Binder et al., 2009). This part of the cortex is also activated during action observation and imitation (Caspers et al., 2010).

The reflection of functional properties of the IPC by its structural subdivisions, in particular in language-related tasks, also provides the rationale to focus on a network analysis approach in bilingual imaging studies with regard to the rostral, the middle and the caudal areas of this part of the cortex. Such an approach paves the way to map the functional connectivity of the IPC subdivisions, involved in bilingual cognitive control – as IPC is an important part of the language control network, mostly functioning in response selection in the face of a conflict (Abutalebi et al., 2013; Green & Abutalebi, 2013; Reverberi et al., 2015) – which thus far has not been addressed in the literature. Therefore, to address this gap in the related state-of-the-art research, we investigated the functional connectivity of the rostral, the middle and the caudal clusters of the IPC with regard to this executive function in bilinguals in a context characterized with language engagement and disengagement. However, delineating the connectivity profiles of all three subareas of the IPC with regard to cognitive control of language is far beyond the scope of this paper. This is because there is a massive amount of results from each part of the IPC and the related discussions for each part need detailed elaborations. Thus, we limited our report to the functional connectivity of the rostral IPC, and the way it is modulated by the task demand, defined in terms of switching to L1 and to L2.

The IPC, the presupplementary motor area (pre-SMA), the prefrontal, and the anterior cingulate cortices (Green & Abutalebi, 2013; Reverberi et al., 2015), in addition to the cerebellum are involved in language control network (Fabebro, Moretti, & Bava, 2000; Green & Abutalebi, 2013). This network supports language control operations, e.g., encoding, intending to use L1 and L2 languages, and resolving competition between languages (Reverberi et al., 2015). Regarding previous studies, the activation of brain areas involved in the language control network is more associated with L2 lexical production; L2 lexical production requires recruitment of more control processes in this network compared to L1 (Garbin et al., 2011; Reverberi et al., 2015); thus, as the IPC is part of the language control network and as L2 lexical production activates more brain areas in that network, our expectation was that in our language switching experiment, switching to L2 would involve stronger positive functional connectivity of the rostral IPC with other parts of the brain in language control network.

In this research, we have benefited from the multiband EPI technique, in which multiple slices are excited and acquired simultaneously. Such an imaging technique is associated with increased sensitivity of BOLD acquisitions (Kundu et al., 2012), the spatial and/or temporal resolution (Chen et al., 2015) and sensitivity in detecting brain functional connectivity (Liao et al., 2013; Preibisch, Castrillón, Bührer, & Riedl, 2015).

3.2 Methods

3.2.1 Participants

Fifty-two, healthy, right-handed students at Leiden University participated in this research. They were 18–27 years old and had normal or corrected-to-normal vision. Based on the information taken from a questionnaire about their language history, these participants were sequential Dutch-English bilinguals, who were not exposed to both Dutch and English from infancy – born to native Dutch parents – and started learning English in primary school. Participants also had regular contact with English because of their academic educations. We measured their English language proficiency by the quick placement test (University of Cambridge Local Examinations Syndicate 2001) (see Table 3.1).

Seven participants were later excluded from the research due to the excessive level of movements in the scanner. Participants gave their written informed consent prior to the experiment and they either were compensated with a small amount of money or received course credits for their participation in this study. The medical ethics committee of Leiden University Medical Center (LUMC) (Leiden, the Netherlands) approved the protocol of this experiment (NL61816.058.17).

Table 3.1

Details of the participants included in the analysis

number of participants	male	female	average age	L2 level	means of measurement	mean score	SD
45	11	34	21.7	upper-inter	placement test	44.17/60	2.23

3.2.2 Stimuli

Forty-eight pictures were selected from the International Picture Naming Project (IPNP- https://crl.ucsd.edu/experiments/ipnp/), based on the following variables in both Dutch and English languages: number of letters and syllables, RT (mean), H statistics which indicates response agreement by participants in naming a picture, initial fricative which indicates if a word starts with a consonant sound such as f or v especially since such words have longer naming latencies (see Bates et al., 2003) and word complexity (see Table 3.2 for a summary of each variable that the stimuli were matched on). We used both the CELEX lexical database and the database provided by IPNP as references for these variables, and we developed two sets of twenty-four stimuli (set A and set B), one set for each language (counterbalanced across participants) which were parallel in terms of all the above-mentioned variables in addition to word frequency, visual complexity and conceptual complexity (see Appendix 3.1 and Appendix 3.2 for further details). Visual complexity as the level of details in an image and conceptual complexity which refers to how many objects, animals or persons are depicted in each image (Snodgrass & Vanderwart, 1980) are the characteristics of images and are independent of a language; thus, these variables were not matched on L1 and L2 but on the two sets of twenty-four stimuli. These two sets were also parallel in terms of the number of cognates; there were nine cognates in each set. The reason that we did not use the same items in L1 and L2 was to avoid the influence of L1 naming on L2 naming and the other way around on the same items.

Table 3.2

Summary of each variable that the stimuli were matched on in L1 & L2 with t-test statistics

Name of variable*	Mean L1	Mean L2	SD L1	SD L2	t	P Value
Number of letters	4.71	4.67	1.43	1.21	0.154	0.878
Number of syllables	1.3	1.33	0.46	0.52	-0.42	0.678
RT (mean)	885.51	849.04	93.81	102.39	1.82	0.072
H statistics	0.23	0.22	1.86	3.28	1.33	0.894
Initial fricative	0.1	0.06	0.31	0.245	7.33	0.465
Word complexity	0.00	0.00	0.00	0.00	**	**

Note. *For a detailed description on the identification of variables see: https://crl.ucsd.edu/experiments/ipnp/method/getdata/uspnovariables.html
**These values could not be computed because the standard deviations of both groups are 0. In fact, no complex words were used.

3.2.3 Procedure

The fMRI experiment included one run of 6 min and 46 s, in an event-related design, using 76 trials. During the experiment participants were required to carry out a language switching task, controlled by E-Prime Software, switching between Dutch (L1) and English (L2). There were two types of trials in four conditions; switch trials in which the cued language was different from the preceding trial (i.e. from Dutch to English or English to Dutch) and non-switch trials in which the language remained the same as the previous trial (i.e. Dutch to Dutch or English to English).

Each trial began with a visual cue for 250 ms, in the form of a red or blue frame (counterbalanced across participants) that preceded a picture and instructed participants which language to use to name the upcoming picture. It was then followed by a fixation cross for 500 ms and presentation of a picture for 2,010 ms.

Each trial ended with a jittered blank screen varying between 690 to 2,760 ms. Optseq program which schedules events in rapid-presentation event-related fMRI experiments was used to pseudo-randomize the order of pictures and to determine the length of each intertrial blank screen interval. In this experiment the switch rate was 50% and the maximum number of stay or switch trials in a row was four.

Before the fMRI data acquisition, participants underwent behavioral training. That included a) familiarization with pictures used in the experiment in which participants in two separate runs saw all pictures with their names one time in Dutch and one time in English, b) learning the association between the visual colored cue and the related language, c) familiarization with a task that was identical to the one used in the fMRI experiment in all respects, but not the target pictures. In order to avoid movement related artifacts, participants were instructed to name pictures with minimal jaw movement. After four weeks, participants attended a behavioral lab and performed the same task that they did inside the MRI scanner, and their responses were collected using an SRBOX. In line with previous research (e.g. Anderson et al., 2018; Grady, Luk, Craik, & Bialystok, 2015) we allowed a few weeks between the experiment in the scanner and the experiment in the behavioral lab to make sure that participants would not remember the stimuli from the first session. In the behavioral lab, E-Prime Software was used to control the presentation of pictures. We collected RTs in the behavioral lab and not in the scanner; however, to make sure that participants carry out the task in the scanner appropriately, they were told that their responses will be monitored by the researcher from the control room.

3.2.4 fMRI data acquisition

All data were acquired on a 3 Tesla Philips Achieva TX MRI scanner in Leiden University Medical Center, equipped with a SENSE-32 channel head coil. Prior to functional images, high-resolution anatomical images were collected for co-registration with the functional ones. These included a 3D gradient-echo T1-weighted sequence with the following parameters: TR = 7.9 ms, TE = 3.5 ms, FA = 8°, FOV = 250 x 195.83 × 170.5, 155 slices 1.1 × 1.1 × 1.1 mm. During the functional run, 555 T2*-weighted whole brain multiband gradient EPIs were acquired, including 6 dummy scans preceding each dynamic scan to allow for equilibration of T1 saturation effects. The scanning parameters regarding the functional run are as follows: TR = 690 ms, TE = 30 ms, multiband factor = 4, FA = 55°, FOV = 220 x 220 x 121, 44 slices 2.75 × 2.75 × 2.75 mm. A high quality BOLD screen 32, that was viewed through a mirror at the head and located at the end of the scanner, was used for visual stimulus presentation.

3.3 Data analysis

3.3.1 Behavioral data analysis

Behavioral data in terms of the reaction time (RT) in performing language switching task in both switch trials in which the cued language was different from the preceding trial (i.e. from Dutch to English or from English to Dutch) and non-switch trials in which the language remained the same as the previous trial (i.e. Dutch to Dutch or English to English) were processed using SPSS software version 23. We used two (language: Dutch vs. English) by two (context: switch vs. non-switch) repeated-measures ANOVA with both subject and item factors – thus running two separate analyses – to see if both context and language would have a main effect with any possible interactions. In addition, we ran subsequent paired t-test to see if in a language switching task, switching to L1 and switching to L2 were significantly different.

3.3.2 Pre-processing of fMRI data

fMRI data were processed using FSL software version 5.0.10 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson, Bannister, Brady & Smith, 2002), non-brain removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). The functional images were registered to MNI-152 standard space (T1-standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) using a three-step registration from functional to high-resolution images, which were registered to T1-weighted structural images, and then registered to the standard space of the MNI template. Registration was carried out using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002).

3.3.3 Psychophysiological interaction (PPI) analysis

We did PPI analysis to examine the functional interaction between the IPC rostral cluster and the rest of the brain. Masks of the IPC rostral cluster right and left were made using the Jülich Histological Atlas. This atlas is implemented within FSLVIEW (www.fmrib.ox.ac.uk/fsl). The probabilistic maps of the right and the left IPC rostral clusters were binarised and thresholded at 50 percent. Then we transformed the masks into the functional space, projecting the ROI on the pre-processed functional images, and extracting the mean time series from the ROI using fslmeants. We did the PPI analyses for the IPC rostral cluster right and left separately using FEAT (FMRI Expert Analysis Tool) version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The design matrix consisted of three regressors. The first regressor was the psychological variable, convolved with a double gamma hemodynamic response and the second regressor, the physiological variable, was the time series extracted from the ROI. The third regressor was the interaction between the psychological and physiological variables (PPI). In these analyses, we tested for significant linear increases and decreases in functional connectivity of the ROI with the rest of the brain during the language switching task with a focus on switch trials.

3.4 Results

3.4.1 Behavioral data

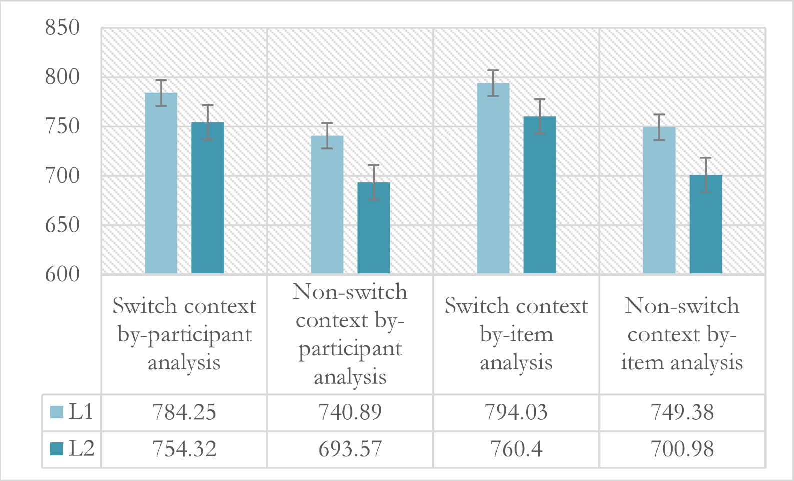
Data from 45 healthy volunteers were analyzed (see Fig. 3.2). Response latencies less than 350 ms and more than 1,500 ms were discarded. In total, the accuracy rate in doing this task - correct responses between 350 ms and 1,500 ms - was 93.8%. Repeated-measures ANOVA showed a significant main effect for context (switch & non-switch) in both by-participants analysis (*F1*(1,44) = 75.63, $P < 0.0001$, partial eta square = 0.63) and in by-item analysis (*F2*(1,47) = 50.69, $P < 0.0001$, partial eta square = 0.52). In the repeated-measures ANOVA the main effect of language (L1 & L2) was significant in both by-participant analysis (*F1*(1,44) = 48.53, $P < 0.0001$, partial eta square = 0.52) and in the by-item analysis (*F2*(1,47) = 29.66, $P < 0.0001$, partial eta square = 0.38). No interaction between language and context was observed (*F1*(1,44) = 3.7, $P = 0.061$, partial eta square = 0.07; *F2*(1,47) = 1.18, $P = 0.282$, partial eta square = 0.025), indicating symmetrical switch costs. These behavioral results are from the data collected four weeks after participants did the experiment inside the scanner.

As there is no interaction between the factors context and language, indicating symmetrical switch costs in Dutch and English, any possibility that the difference in participants' reaction times (RTs) between switch trials and non-switch trials in the stronger language (Dutch/L1) or the weaker language (English/L2) is differently influenced by the context can be ruled out. According to Fig. 3.2, the weaker language is quicker in both switch and non-switch trials. These results are in line with previous research (Christoffels, Firk & Schiller, 2007; Costa & Santesteban, 2004; Gollan & Ferreira, 2009; Verhoef, Roelofs, & Chwilla, 2009) and is presumably due to more suppression of the stronger language in language switching in order to speak in the weaker language - retrieving the more inhibited language is more effortful (for more details, see Green, 1998).

The subsequent paired *t*-test also showed that in the language switching task, switching to L1 was significantly slower than switching to L2 ($t1$(44) = -3.859, $P < 0.0001$; $t2$(47) = -3.326, $P < 0.002$). As number of letters and syllables, RT (mean), H statistics, initial fricative, morphological complexity, and word frequency were matched across stimuli in both languages, any possibility that a language might have suffered or benefited more than the other language due to more difficult or easier stimuli can also be ruled out.

Figure 3.2

L1 and L2 RTs in millisecond in the switch and non-switch contexts in both the by-participants and the by-item analyses



Note. As shown in this figure, in both switch and non-switch contexts L2 lexical production is quicker than L1 lexical production, with symmetrical switch costs.

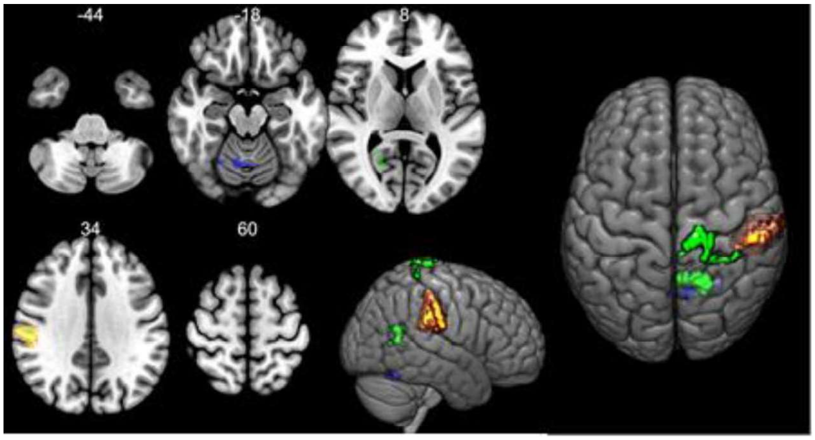
3.4.2 PPI results

3.4.2.1 PPI results from switching to L1

Having created masks of the IPC rostral cluster right and left, we investigated the interaction between the psychological variable (time series associated with L1 switch trials, convolved with a double gamma hemodynamic response) and the physiological variable (time series extracted from the ROI).

Figure 3.3

Showing clusters, that the right IPC rostral cluster has functional connectivity with, as a result of switching to L1.

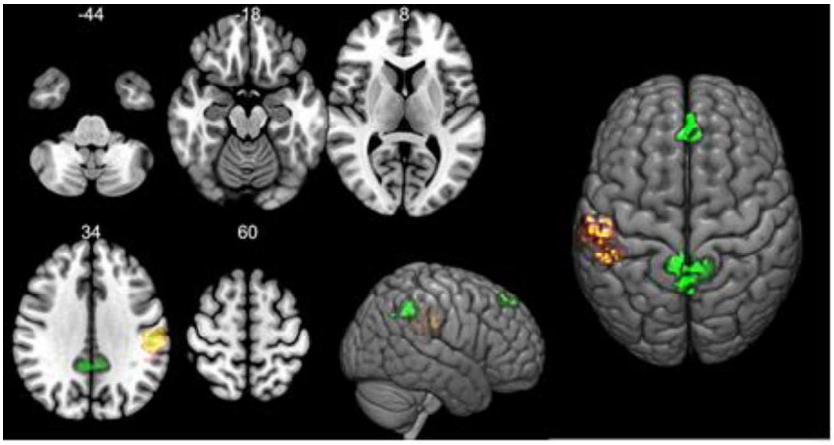


Note. In this figure, the location of the right IPC rostral cluster, as the seed region, is shown in yellow-red. The green color demonstrates brain areas, localized in the precuneus cortex and in the postcentral gyrus, that the right rostral IPC has negative functional connectivity with. The blue color shows a cluster localized in the cerebellum, posterior lobe, that the right rostral IPC has positive functional association with.

We tested for significant linear increases and decreases in the functional connectivity of the ROI with the rest of the brain. Z statistic images were thresholded non-parametrically using clusters determined by Z > 3.1 and a (corrected) cluster significance threshold of P < 0.05. Clusters with fewer than 10 active voxels were excluded. When participants switched to L1, there was a significant linear increase in the functional connectivity between a cluster localized in the right cerebellum, posterior lobe, declive, and the right IPC rostral cluster. In addition, we observed significant linear decreased coupling between the right IPC rostral cluster and two other clusters; one cluster was localized in the precuneus cortex and the other cluster was localized in the postcentral gyrus (see Table 3.3 and Fig. 3.3).

Figure 3.4

Showing clusters, that the left IPC rostral cluster has functional connectivity with, as a result of switching to L1.



Note. In this figure, the location of the left IPC rostral cluster, as the seed region, is shown in yellow-red. The green color demonstrates brain areas, localized in the precuneus cortex and the superior frontal gyrus, that the left rostral IPC has negative functional connectivity with.

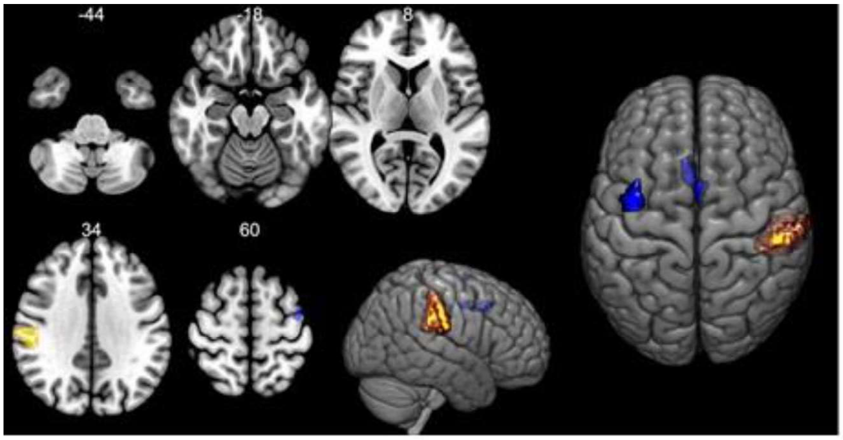
Regarding the functional associations between the left IPC rostral cluster and other parts of the brain under the effect of switching to L1, we observed no positive psychophysiological interactions; however, there were negative couplings between the left IPC rostral cluster and two clusters localized in the precuneus cortex and the superior frontal gyrus (see Table 3.3 and Fig. 3.4).

3.4.2.2 PPI results from switching to L2

In a separate analysis, we also investigated the interaction between time series associated with L2 switch trials and the time series extracted from the ROI, to see if significant linear increases and decreases in the functional connectivity of the ROI and the rest of the brain could be detected. Z (Gaussianised T/F) statistic images were thresholded non-parametrically using clusters determined by $Z > 3.1$ and a (corrected) cluster significance threshold of $P < 0.05$. Clusters with fewer than 10 active voxels were excluded. Under the effect of switching to L2, positive correlation in the activity of the right IPC rostral cluster was observed with a cluster localized in the cingulate gyrus anterior division. In addition, in this condition we observed another positive coupling between the right IPC rostral cluster and a cluster localized in the precentral gyrus. No negative functional association between the ROI and any other cluster was detected in trials requiring participants to switch to L2 (see Table 3.3 and Fig. 3.5).

Figure 3.5

Showing clusters, that the right IPC rostral cluster has functional connectivity with, as a result of switching to L2.



Note. In this figure, the location of the right IPC rostral cluster, as the seed region, is shown in yellow-red. The blue color demonstrates brain areas, localized in the cingulate gyrus anterior division, and in the precentral gyrus, that the right rostral IPC has positive functional connectivity with.

Finally, we observed no positive or negative coupling between the left IPC rostral cluster and other brain areas under the effect of switching to L2.

Table 3.3

Clusters that the rostral cluster IPC R/L has functional connectivity with, when switching to L1/L2.

Clusters	Switch L1/L2	Voxels	Coupling	Z-Max	R/L Seed	Location (MNI) X Y Z
Cerebellum, posterior lobe	L1	125	positive	4.19	R	15.8, -60.8, -20.4
Postcentral gyrus	L1	147	negative	4.13	R	20.5, -34.6, 76.5
Precuneus cortex	L1	254	negative	5.18	R	15.8, -55.1, 17.7
Superior frontal gyrus	L1	120	negative	4.05	L	2.44, 38.2, 48.3
Precuneus cortex	L1	475	negative	4.6	L	4.28, -48.1, 39.9
Cingulate gyrus, anterior division	L2	99	positive	3.91	R	-2.01, 9.28, 40.7
Precentral gyrus	L2	118	positive	4.3	R	-39.5, -4.15, 63.7

3.5 Discussion

In this study, we focused on the functional connectivity of the rostral IPC with other parts of the brain with regard to cognitive control of language. For this reason, we used a language switching task paradigm, in which language engagement and disengagement in two contexts associated with higher cognitive demand (switching to L1) and lower cognitive demand (switching to L2) is a key factor. In a language switching paradigm, the stronger language (Dutch/L1) is more inhibited in order to speak in the weaker language (English/L2), and hence retrieving the more inhibited language is cognitively more demanding. We observed in our behavioral results that reaction times for L1 (across the board for switch and non-switch trials) were slower, in line with previous research (Christoffels et al., 2007; Costa & Santesteban, 2004; Ghafar Samar, Tabassi Mofrad, & Akbari, 2014; Gollan & Ferreira, 2009; Tabassi Mofrad, Ghafar Samar, & Akbari, 2015, 2017; Verhoef et al., 2009).

With regard to our fMRI findings, the functional associations of the rostral IPC did not follow the same patterns in switching to L1 and in switching to L2. That is, cognitive demand modulated the patterns of the functional connectivity of this part of the cortex – accompanied with laterality differences – with other brain areas. In the following we elaborate on the connectivity patterns of the rostral IPC in both switching to L1 and switching to L2, and how each functional association of this brain area is defined in these conditions with respect to the previous studies.

3.5.1 Switching to L1

In this research, we observed negative couplings, that is negative associations of both the right and the left IPC rostral clusters with the precuneus cortex in switching to L1. The precuneus cortex is part of default mode network (DMN) (Smith et al., 2009). This network is mostly reported to modulate executive functions via its reduced amount of functional connectivity (Dang, O'Neil, & Jagust, 2013). Moreover, according to Gilbert, Bird, Frith, and Burgess (2012), the more difficult a task is, defined in terms of more error rates and slower reaction times, the more suppression in the activity of the precuneus, the bilateral IPC as well as left middle frontal gyrus would be observed. The negative functional connectivity of both the right and the left IPC rostral clusters with precuneus cortex in the more cognitively demanding context, in our study, not only points to the previous accounts on the general function of the precuneus and the bilateral IPC in the face of a more difficult task, but also demonstrates the co-functioning of these parts of the cortex – the right and the left IPC rostral cluster with the precuneus – to meet task demands.

The other brain areas that the rostral IPC has functional connectivity with when switching to L1 are the superior frontal and the right postcentral gyri. The superior frontal is recognized to bring about a facilitating processing manner via its top-down bias mechanisms when irrelevant candidates compete with those representations which are related to a task (Miller & Cohen, 2001) and it has strong interconnections with the parietal cortex (Petrides & Pandya, 1984). Such a circuit has been reported to play a role when there is a need to select among competing responses, with the left parietal cortex engaged in activating responses which are possible, and the prefrontal cortex involved in selecting a response among competing candidates (Bunge et al., 2002). Results from our study corroborate the interconnections between the prefrontal cortex and the parietal cortex, however, in a more detailed way as we observed this interconnection between the superior frontal gyrus or rather the superior part of the prefrontal cortex and the left part of the rostral IPC. In our study both switching to L1 and switching to L2 necessitate selecting a response among competing candidates, however, the interconnection between the superior frontal gyrus and the left rostral IPC is only observed when switching to L1. Furthermore, this interconnection is defined in terms of the negative coupling between these two parts of the cortex. Therefore, it seems that this circuit is more evident when response selection is more challenging, however, the nature of such coupling involved in this circuit needs more research.

Regarding the postcentral gyrus, this part of the cortex is the location of the primary somatosensory cortex which is involved in executive functions (EFs). According to Reineberg et al. (2015) in individuals with better performance in EFs, when resting state functional connectivity is concerned, the fronto-parietal network in which the inferior parietal cortex is a major component, is more extended due to connectivity with nodes outside of this network, in particular with somatosensory regions. Tabassi Mofrad, Jahn and Schiller (2019), and Tabassi Mofrad and Schiller (2019), moreover, by investigating resting state networks involved in EFs reported the connectivity of the primary somatosensory cortex with the fronto-parietal network.

Research into brain functional connectivity architecture shows that there is a high correspondence between brain regions involved in both task-related and resting state functional connectivity (Fair et al., 2007) and that brain regions that work together to accomplish a particular task also fluctuate together when resting state functional connectivity is concerned (Cole et al., 2014; Smith et al., 2009). In fact, the intrinsic network architecture characterized during the resting state, shapes the architecture of brain functional networks involved in performing a task; hence, there is a strong association between the two (Cole et al., 2014), though the resting state functional associations have reverse activation during task-related brain functional connectivity. In our study, we observed the negative functional connectivity of the postcentral gyrus as the location of the primary somatosensory cortex, with the right IPC rostral cluster since this study concerns task-related functional associations. Moreover, as we observed such coupling only in switching to L1, we assume that this association is characterized with challenging conditions.

The other point in brain functional associations when switching to L1 regards the positive coupling the right IPC rostral cluster with the cerebellum, the posterior lobe, declive. The involvement of the cerebellum in EFs is not yet well understood and debated in the literature; however, it is emphasized that the cerebellum contributes to the higher order cognitive functions, though its contribution to EFs might be different from brain areas involved in the frontoparital network (Bellebaum & Daum, 2007). Moreover, it is also reported that the cerebellum is linked to the language control network regions, e.g. the inferior frontal cortex (Green & Abutalebi, 2013; Krienen & Buckner, 2009) to process morphosyntactic features in speech production (Marien, Engelborghs, Fabbro, & De Deyn, 2001) - For a review see Tyson, Lantrip, and Roth (2014). Although more research is needed to better understand the contribution of the cerebellum to EFs, we have at least shown its involvement in cognitive control of language via the positive coupling of the right IPC rostral cluster with this brain area when the context is cognitively more demanding.

3.5.2 Switching to L2

In the current research, we observed that the right IPC rostral cluster has positive functional connectivity with the ACC and the precentral gyrus when switching to L2. Generally, ACC contributes to response selection and it monitors conflicts between languages (Abutalebi et al., 2012). It is reported that in the process of response selection, ACC identifies the conflict among competing cues, then the prefrontal cortex via a signal received from ACC on the existence of a conflict, modulates control provided by the top-down regulatory mechanisms of the posterior cortex or the basal ganglia (MacDonald et al., 2000). In our study, switching to L2 is also associated with quicker responses, or rather shorter RTs; moreover, such positive association of the ACC and the right IPC rostral cluster is only observed in switching to L2. As the inferior parietal areas are also involved in response selection (Abutalebi et al., 2008), the positive coupling or rather the positive association of the right IPC rostral cluster with the ACC, in our study, indicates a strong response selection circuit involved in switching to L2, presumably responsible for shorter RTs in this context. Furthermore, as ACC is part of the language control network (Abutalebi & Green, 2008, 2016), that positive association points to our expectation of the research results.

Regarding the involvement of the precentral gyrus in switching to L2, the right part of the seed region has positive functional connectivity with this brain area. Precentral gyrus is generally reported to be involved in response inhibition (Bunge et al., 2002) and task RT (McGuire & Botvinick, 2010). In particular, in language studies, it is emphasized that the precentral gyrus contributes to language switching though the conditions of this task e.g. switching to L1 or switching to L2, in which this part of the cortex plays a role, is not differentiated (Hernandez, 2009; Luk, Anderson, Craik, Grady, & Bialystok, 2012). Moreover, without specifying the nature of the functional association of the precentral gyrus with other parts of the brain, it is reported that in language switching the fronto-parietal network is extended to precentral gyrus (Ma et al., 2014).

With respect to the results from our study, we elaborate that the right IPC rostral cluster, which is part of the fronto-parietal network, is extended to precentral gyrus via a positive functional coupling in language switching but only in switching to L2. As this condition is associated with shorter RTs, and as the precentral gyrus is also involved in response inhibition (Bunge et al., 2002) and task RT (McGuire & Botvinick, 2010), we assume that coupling of the right IPC rostral cluster, a sub area of the inferior parietal areas whose function in response selection have been repeatedly reported in the literature (Abutalebi et al., 2008; Branzi et al., 2016), with the precentral gyrus points to the underlying cognitive mechanisms with a facilitatory function in this language condition.

3.5.3 Laterality differences

According to the results of our research, not only task demand modulates the patterns of functional connectivity of the rostral IPC with other parts of the brain, but also it brings about the laterality differences of this part of the cortex. In switching to L2, only the right rostral IPC is involved in positive associations with ACC and the precentral gyrus. However, in switching to L1 the right and the left IPC rostral clusters showed negative functional coupling with the postcentral gyrus, and the precuneus cortex in the former and with the superior frontal gyrus and the precuneus cortex in the latter. The only positive functional connectivity in this condition regards the coupling of the right part of the rostral IPC with the cerebellum, the posterior lobe.

Regarding the laterality differences of the IPC as a whole, in previous research the left IPC is associated with language processing, in particular with semantic and phonological processing (Bzdok et al., 2016; Price, 2012; Vigneau et al., 2006). Moreover, in studies of bilingual aphasia damage to the left IPC is assumed to cause uncontrolled switching between languages (Fabbro, Skrap, & Aglioti, 2000; Khateb et al., 2007). The left IPC in healthy participants is also associated with language switching. According to Wang, Kuhl, Chunhui, and Dong (2009), language switching trials activated the left IPC, though the direction of the language switch was not differentiated in this comparison. The right IPC, however, is mostly reported to be involved in social cognition (Decety & Lamm, 2007; Koster-Hale, Saxe, Dungan, & Young, 2013), auditory spatial attention (Karhson, Mock, & Golob, 2015) and the presentation of deviant sounds (Schönwiesner et al., 2007). Although previous studies have not reported the involvement of the right IPC in language processing and in particular in language switching behavior, in the current study, by using a functional connectivity analysis, we have shown that both the right and the left IPC rostral clusters via positive or negative couplings with other parts of the cortex are involved in language switching. The nature of each coupling depending on switching to L1 and switching to L2 differentiated the functions of the right and the left IPC rostral clusters in this regard.

To recapitulate, with respect to the results of this research, switching to L1 requires bilateral recruitment of the rostral IPC, whereas in switching to L2 only the right IPC rostral cluster is involved. Consequently, we are of the opinion that recruiting more underlying neural processes in switching to L1, along with the function of connectivity patterns of the right and the left rostral IPC associated with this language condition, points to the more cognitively demanding nature of switching to L1. Consistent with this line of argument, the less cognitively demanding characteristic of switching to L2, marked with shorter RTs than those of L1, only necessitated the involvement of the right rostral IPC.

3.6 Conclusion

In this study, we focused on how the rostral IPC contributes to cognitive control of language, that is the cognitive mechanisms that enable bilinguals to avoid interference from a non-target language when they utter a word in an intended language (Abutalebi & Green, 2007; Green & Abutalebi, 2013). In doing so, we concentrated on how the rostral IPC adopts different functional connectivity patterns in a context characterized with language engagement and disengagement which recruits the neural mechanisms of cognitive control (Abutalebi & Green, 2008). In our study, we also focused on how cognitive demand - defined in terms of switching to L1 which is cognitively more demanding and switching to L2 which is cognitively less demanding - manipulates such brain functional connectivity in order to meet task demands. By mapping connectivity patterns of the rostral IPC involved in cognitive control of language, we have shown that this part of the cortex adopts asymmetrical patterns of functional connectivity when cognitive demand is concerned and how such functional associations contribute to cognitive control of language. Lastly, according to our research results in language switching behavior both the right and the left IPC rostral clusters are involved, with switching to L1 recruiting the bilateral rostral IPC and with switching to L2 requiring only the involvement of the right rostral IPC.

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Appendix 3.1

*Summary of each variable that the stimuli were matched on in set A & B with regard to L1**

Name of variable**	Mean Set A	Mean Set B	SD Set A	SD Set	t	P Value
Number of letters	4.71	4.71	1.27	1.6	0.00	1.00
Number of syllables	1.25	1.33	0.44	0.48	-0.62	0.54
RT (mean)	885.86	885.16	87.45	101.67	0.024	0.981
H statistics	0.23	0.23	0.17	0.2	0.004	0.997
Initial fricative	0.08	0.13	0.28	0.34	-0.44	0.664
Word frequency	1.5	1.6	0.54	0.63	-0.631	0.534
Visual complexity	17521.63	16857.21	7320.9	8299.79	0.27	0.79
Conceptual complexity	1.17	1.25	0.48	0.61	-0.492	0.627
Word complexity	0.00	0.00	0.00	0.00	***	***

Note. *Set A and set B refer to the two sets of twenty-four stimuli.

**Visual complexity and conceptual complexity were matched on set A and B with respect to characteristics of the images and independent of L1.

***These values could not be computed because the standard deviations of both groups are 0.

Appendix 3.2

Summary of each variable that the stimuli were matched on in set A & B with regard to L2

Name of variable**	Mean Set A	Mean Set B	SD Set A	SD Set	t	P Value
Number of letters	4.75	4.58	1.33	1.1	0.59	0.57
Number of syllables	1.38	1.3	0.58	0.46	0.62	0.54
RT (mean)	854.5	843.58	87.73	116.88	0.36	0.73
H statistics	0.27	0.18	0.4	0.23	0.93	0.36
Initial fricative	0.08	0.04	0.28	0.2	0.57	0.58
Word frequency	3.73	3.82	1.11	1.2	-0.24	0.81
Visual complexity	17521.63	16857.21	7320.9	8299.79	0.27	0.79
Conceptual complexity	1.17	1.25	0.48	0.61	-0.492	0.627
Word complexity	0.00	0.00	0.00	0.00	**	**

Note. *Visual complexity and conceptual complexity were matched on set A and B with respect to characteristics of the images and independent of L2.
** These values could not be computed because the standard deviations of both groups are 0.

Chapter 4

Mapping caudal inferior parietal cortex supports the hypothesis about a modulating cortical area

This chapter is based on:

Tabassi Mofrad, F., & Schiller, N. O. (2022). Mapping caudal inferior parietal cortex supports the hypothesis about a modulating cortical area. *NeuroImage*, *259*, 119441.

Abstract

The cytoarchitectonically tripartite organization of the inferior parietal cortex (IPC) into the rostral, the middle and the caudal clusters has been generally ignored when associating different functions to this part of the cortex, resulting in inconsistencies about how IPC is understood. In this study, we investigated the patterns of functional connectivity of the caudal IPC in a task requiring cognitive control, using multiband EPI. This part of the cortex demonstrated functional connectivity patterns dissimilar to a cognitive control area and at the same time the caudal IPC showed negative functional associations with both task-related brain areas and the precuneus cortex, which is active during resting state. We found evidence suggesting that the traditional categorization of different brain areas into either task-related or resting state-related networks cannot accommodate the functions of the caudal IPC. This underlies the hypothesis about a new brain functional category as a modulating cortical area proposing that its involvement in task performance, in a modulating manner, is marked by deactivation in the patterns of functional associations with parts of the brain that are recognized to be involved in doing a task, proportionate to task difficulty; however, its patterns of functional connectivity in some other respects do not correspond to the resting state-related parts of the cortex.

4.1 Introduction

The inferior parietal cortex (IPC) has long been reported to be involved in action-related functions (Keysers & Gazzola, 2009; Caspers et al., 2010), detection of visual target and novelty (Gur et al. 2007), flexible reconfiguration of behavior (Singh-Curry & Husain, 2009) and in particular in cognitive control of language which engages parts of the cortex involved in general aspects of cognitive control (Abutalebi & Green, 2007, 2008; Branzi et al., 2016). The IPC is in fact considered part of the language control network (Fabbro, Moretti, & Bava, 2000; Green & Abutalebi, 2013) that supports language control functions such as resolving competition between languages (Reverberi et al., 2015) and switching between languages (Abutalebi & Green, 2008; Kroll et al., 2006).

Based on the structural parcellation of the human IPC, this part of the cortex consists of three clusters, namely the rostral, the middle and the caudal (Caspers et al., 2013). The white matter connectivity of the IPC as well as the functional differentiations of this part of the cortex also point to the IPC's cytoarchitectonically different areas (Caspers et al., 2013; Corbetta et al., 2008; Keysers & Gazzola, 2009). Regarding the fiber tracks between the IPC clusters and other parts of the cortex, Caspers et al. (2011) reported that the IPC rostral cluster has connections with the somatosensory areas, motor and premotor cortex as well as with the inferior frontal cortex. The IPC caudal cluster is connected with the temporal and the higher visual areas in addition to the posterior parietal cortex. The IPC middle cluster, however, has strong connections with the superior parietal cortex, the intraparietal areas and with the frontal cortex, demonstrating similarities in white matter connectivity with both those of the rostral and the caudal IPC. Having said that, in delineating the contribution of the IPC to different cognitive functions, in particular to cognitive control including response selection (Branzi et al., 2016) updating, shifting and inhibition (Abutalebi & Green, 2008; Wager, Jonides, & Reading, 2004), attention (Corbetta, Patel & Shulman, 2008;

Tomasi & Volkow, 2011) and memory (Martinelli et al., 2013), the IPC is considered as a whole, regardless of its tripartite organization into the rostral, the middle and the caudal clusters. In other words, in reporting the involvement of the IPC in cognitive control and the importance of this part of the cortex in frontoparietal network (for a review see Dajani & Uddin, 2015), the literature has ignored the fact that every part of the tripartite section of the IPC has some functional characteristics related to its structural organization and depending on the type of task, the rostral, the middle and the caudal IPC can have different functional associations with other parts of the brain. Thus, it is possible that it is not the whole IPC that contributes to cognitive control but one or two parts of its tripartite organization, or if all three parts of the IPC contribute to cognitive control, they might not have the same activity and functional connectivity patterns.

As part of our comprehensive project to map the functional connectivity patterns of the IPC clusters, we have already reported the involvement of the rostral IPC in cognitive control of language and have highlighted that cognitive demand modulates connectivity patterns of this part of the cortex (Tabassi Mofrad & Schiller, 2020). In mapping the connectivity patterns of the caudal IPC, we followed an exploratory approach since to our knowledge there are no previous studies in which functional connectivity patterns of the caudal IPC in task performance are addressed, based on which one could formulate a hypothesis in the context of the related literature.

Regarding the activation (but not the connectivity patterns) of the angular gyrus, Wu et al. (2009) reported that this part of the cortex was strongly deactivated in performing the mental arithmetic tasks with Arabic and Roman numerals. The angular gyrus, which is subdivided into the two subregions, namely, PGa and PGp is identical to the caudal IPC when using correlated transmitter receptor-based organization of the IPC (Caspers et al. 2006, 2008 & 2013). In some other studies the angular gyrus is implicated in numerous tasks and processes (for a review see Seghier, 2013; Ramanan & Bellana 2019). The IPC is also questionably considered part of the resting state network e.g. Shehzad et al. (2009) reported that the IPC is a task-deactivated area though the involvement of the IPC in different cognitive functions cannot be ignored.

As mentioned earlier, the inconsistencies in reporting the functions of the IPC are by far due to considering this part of the cortex as a whole and attributing functions of different IPC sub-areas to the whole IPC. Such contradictory reports gave us the hint of a possibility that the caudal IPC might show connectivity patterns different from what could be expected from the general behavior of the IPC as a whole, when task involvement is concerned.

In this project, we benefited from the multiband EPI technique (multiband factor = 4) with one of the quickest repetition time (TR = 690 ms) in image acquisition, resulting in increasing the sensitivity in mapping brain functional connectivity (Liao et al., 2013; Preibisch et al., 2015), increasing the temporal and the spatial resolution (Chen et al., 2015), and increasing the sensitivity of BOLD acquisitions (Kundu et al., 2012).

4.2 Methods

4.2.1 Participants

Fifty-two students from Leiden University aged 18-27 years took part in this study. They were Dutch-English bilinguals with upper-intermediate proficiency in English, healthy and right-handed with normal or corrected-to-normal vision. We did not use the data from seven participants because of their excessive movements in the scanner, so the final composition of the participants was 34 females and 11 males. Participants gave their written informed consent before taking part in the experiment and they were either remunerated or received course credits for their participation. We received the approval of the medical ethics committee of Leiden University Medical Center (LUMC) (Leiden, the Netherlands) for the protocol of this experiment (NL61816.058.17).

4.2.2 Stimuli

We selected forty-eight pictures from the International Picture Naming Project (IPNP- https://crl.ucsd.edu/experiments/ipnp/) based on the following variables in both Dutch and English: RT (mean), number of letters and syllables, initial fricative, H statistics, and word complexity (see Table 4.1 for a summary of the variables).

Table 4.1

Summary of each variable that the stimuli were matched on in L1 & L2 with t-test statistics

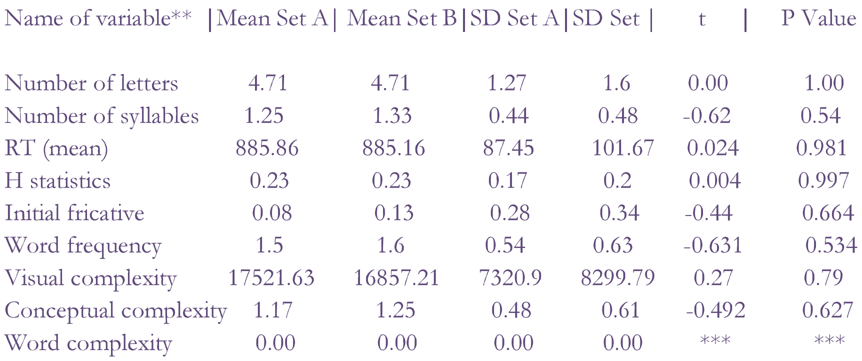
Name of variable*	Mean L1	Mean L2	SD L1	SD L2	t	P Value
Number of letters	4.71	4.67	1.43	1.21	0.154	0.878
Number of syllables	1.3	1.33	0.46	0.52	-0.42	0.678
RT (mean)	885.51	849.04	93.81	102.39	1.82	0.072
H statistics	0.23	0.22	1.86	3.28	1.33	0.894
Initial fricative	0.1	0.06	0.31	0.245	7.33	0.465
Word complexity	0.00	0.00	0.00	0.00	**	**

Note. *For a detailed description on the identification of variables see: https://crl.ucsd.edu/experiments/ipnp/method/getdata/uspnovariables.html
**These values could not be computed because the standard deviations of both groups are 0. In fact, no complex words were used.

Both CELEX lexical database as well as the IPNP database were used as references for the variables summarized in Table 4.1. We developed two parallel sets of twenty-four stimuli, namely, set A and set B, which we counterbalanced across participants, having considered all the variables in Table 4.1 in addition to visual complexity, conceptual complexity and word frequency (see Table 4.2 and Table 4.3 for further details).

Table 4.2

*Summary of each variable that the stimuli were matched on in sets A & B with regard to L1**



Name of variable**	Mean Set A	Mean Set B	SD Set A	SD Set	t	P Value
Number of letters	4.71	4.71	1.27	1.6	0.00	1.00
Number of syllables	1.25	1.33	0.44	0.48	-0.62	0.54
RT (mean)	885.86	885.16	87.45	101.67	0.024	0.981
H statistics	0.23	0.23	0.17	0.2	0.004	0.997
Initial fricative	0.08	0.13	0.28	0.34	-0.44	0.664
Word frequency	1.5	1.6	0.54	0.63	-0.631	0.534
Visual complexity	17521.63	16857.21	7320.9	8299.79	0.27	0.79
Conceptual complexity	1.17	1.25	0.48	0.61	-0.492	0.627
Word complexity	0.00	0.00	0.00	0.00	***	***

Note. *Set A and set B refer to the two sets of twenty-four stimuli.

**Visual complexity and conceptual complexity were matched on set A and B with respect to characteristics of the images and independent of L1.

***These values could not be computed because the standard deviations of both groups are 0

Table 4.3

Summary of each variable that the stimuli were matched on in sets A & B with regard to L2

Name of variable**	Mean Set A	Mean Set B	SD Set A	SD Set	t	P Value
Number of letters	4.75	4.58	1.33	1.1	0.59	0.57
Number of syllables	1.38	1.3	0.58	0.46	0.62	0.54
RT (mean)	854.5	843.58	87.73	116.88	0.36	0.73
H statistics	0.27	0.18	0.4	0.23	0.93	0.36
Initial fricative	0.08	0.04	0.28	0.2	0.57	0.58
Word frequency	3.73	3.82	1.11	1.2	-0.24	0.81
Visual complexity	17521.63	16857.21	7320.9	8299.79	0.27	0.79
Conceptual complexity	1.17	1.25	0.48	0.61	-0.492	0.627
Word complexity	0.00	0.00	0.00	0.00	**	**

Note. *Visual complexity and conceptual complexity were matched on set A and B with respect to characteristics of the images and independent of L2.
** These values could not be computed because the standard deviations of both groups are 0.

4.2.3 Procedure

We used a language switching task, which requires cognitive control, with two levels of cognitive demand (switching to the first language (L1) is cognitively more demanding than switching to the second language (L2)) to map the functional connectivity of the caudal IPC. During the experiment, participants were required to do a language switching task that we controlled by the E-Prime Software, and they switched between Dutch (L1) and English (L2). The experiment included two types of trials in four conditions. There were either switch trials in which the response language was different from the preceding trial (i.e. from Dutch to English or English to Dutch) or non-switch trials in which the response language remained the same as the previous trial (i.e. Dutch to Dutch or English to English). The fMRI experiment included one run of 6 min and 46 s, in an event-related design. Each trial began with a visual cue for 250 ms, in the form of a red (for Dutch) or blue frame (for English), which was counterbalanced across participants, and preceded a picture to instruct participants which language to use to name the upcoming picture. The cue was followed by a fixation cross for 500 ms and then by presentation of a picture for 2,010 ms, the order of which was pseudo-randomized. Each trial ended with a jittered blank screen varying between 690 to 2,760 ms.

Participants first underwent a behavioral training before the fMRI data acquisition. During the training, participants were familiarized with pictures used in the experiment, learned the association between the color cue and the response language and did a small scale of a language switching task in which the target pictures were not used. We instructed participants to name pictures with minimal jaw movement to avoid movement-related artifacts. Four weeks after the fMRI data acquisition session, participants attended the behavioral lab and did the same task that they performed inside the MRI scanner. We collected their responses using an SRBOX, in line with previous studies (e.g. Anderson et al., 2018; Grady et al., 2015).

4.2.4 fMRI data acquisition

We acquired all the data on a 3 Tesla Philips Achieva TX MRI scanner in the Leiden University Medical Center, which was equipped with a SENSE-32 channel head coil. First, we collected the high-resolution anatomical images for co-registration with the functional ones, before the functional images were acquired. The high-resolution anatomical images included a 3D gradient-echo T1-weighted sequence with the following parameters: TR = 7.9 ms, TE = 3.5 ms, FA = 8°, FOV = 250 x 195.83 x 170.5, 155 slices $1.1 \times 1.1 \times 1.1$ mm^3. We also acquired 555 T2*-weighted whole brain multiband gradient EPIs, preceded by 6 dummy scans to allow for equilibration of T1 saturation effects. The scanning parameters regarding the functional run are as follows: TR = 690 ms, TE = 30 ms, multiband factor = 4, FA = 55°, FOV = 220 x 220 x 121, 44 slices 2.75 × 2.75 × 2.75 mm^3. To present visual stimuli, we used a high-quality BOLD screen 32 located at the end of the scanner that participants viewed through a mirror at their head.

4.3 Data analysis

4.3.1 Behavioral data analysis

We processed the behavioral data by using SPSS software version 23. Behavioral data included the reaction time (RT) in doing the language task switching - the switch trials (i.e. from Dutch to English or from English to Dutch) and non-switch trials (i.e. Dutch to Dutch or English to English). A two (language: Dutch vs. English) by two (context: switch vs. non-switch) repeated-measures ANOVA was used to analyze the effect of both context and language, followed by paired *t*-test to examine whether in a language switching task, switching to L1 and switching to L2 were significantly different.

4.3.2 Pre-processing of fMRI data

We processed the fMRI data using FSL software version 5.0.10 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) and we applied the following pre-statistics processing: motion correction using MCFLIRT (Jenkinson et al., 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, non-brain removal using BET (Smith, 2002), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). We registered the functional images to MNI-152 standard space (T1-standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) by a three-step registration from functional to high-resolution images, which were registered to T1-weighted structural images, and then registered to the standard space of the MNI template. We carried out the registration of functional images to MNI-152 standard space by using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002).

4.3.3 Psychophysiological interaction (PPI) analysis

To examine the functional connectivity of the caudal IPC with other parts of the brain, we did PPI analyses. In doing so, we created masks of the right and the left IPC caudal cluster by using the Jülich Histological Atlas, implemented in FSL. We binarised the probabilistic maps of the right and the left IPC caudal cluster and thresholded them at 50 percent. Masks were then transformed into the functional space and we projected the ROI on the pre-processed functional images and extracted the mean time series from the ROI by using fslmeants. We did separate PPI analyses for the right and left IPC caudal clusters using FEAT (FMRI Expert Analysis Tool) version 6.00. Our design matrix included three regressors. One of the regressors was the physiological variable which was the time series that we extracted from the ROI. The other regressor was the psychological variable convolved with a double gamma hemodynamic response. The third regressor was the interaction between the physiological and the psychological variables (PPI). By doing PPI analyses, we tested for the significant linear decreases and increases in functional connectivity of the right and the left caudal IPC with other parts of the brain when participants switched to L1 and to L2. We also did separate PPI analyses using the fMRI data from only female participants as sensitivity analyses, to test to what extent the results could be affected.

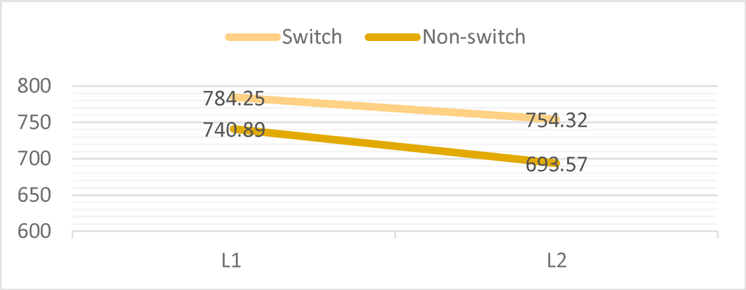
4.4 Results

4.4.1 Behavioral data

After having discarded RTs of less than 350 ms and more than 1,500 ms, repeated-measures ANOVA demonstrated a significant main effect for language (L1 & L2) ($F1(1,44) = 48.53$, $P < 0.0001$, partial eta square = 0.52) and for context (switch & non-switch) ($F1(1,44) = 75.63$, $P < 0.0001$, partial eta square = 0.63), with no interaction between language and context (*F1*(1,44) = 3.7, *P* = 0.061, partial eta square = 0.07) which indicated symmetrical switch costs (see Fig. 4.1 for a summary of the behavioral data).

Figure 4.1

L1 and L2 RTs in millisecond in switch and non-switch contexts



Note. As shown in this figure, in both switch and non-switch contexts L2 lexical production is quicker than L1 lexical production.

Due to suppression of the stronger language (L1) in language switching task in order to speak in the weaker language (L2), and since retrieving the more inhibited language is more effortful (Green, 1998), the stronger language is slower in both switch and non-switch trials, in line with previous studies (Christoffels, Firk & Schiller, 2007; Ghafar Samar, Tabassi Mofrad, & Akbari, 2014; Gollan & Ferreira, 2009; Tabassi Mofrad, Ghafar Samar, & Akbari, 2015, 2017). The paired *t*-test also demonstrated that switching to L1 was significantly slower than switching to L2 (*t1*(44) = -3.859, *P* < 0.0001; *t2*(47) = -3.326, *P* < 0.002), and that highlights the more cognitively demanding nature of retrieving the lexicons of the stronger language, in a language switching context.

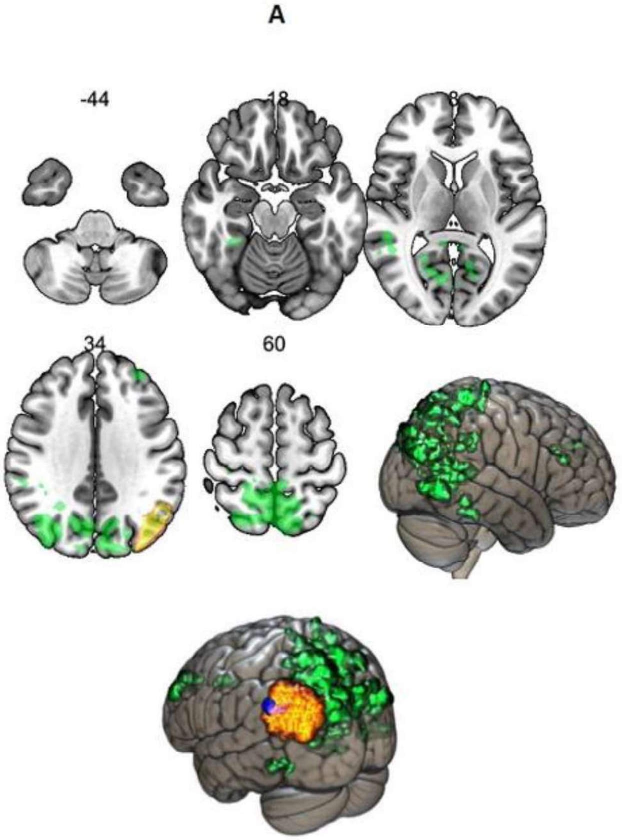
4.4.2 PPI results

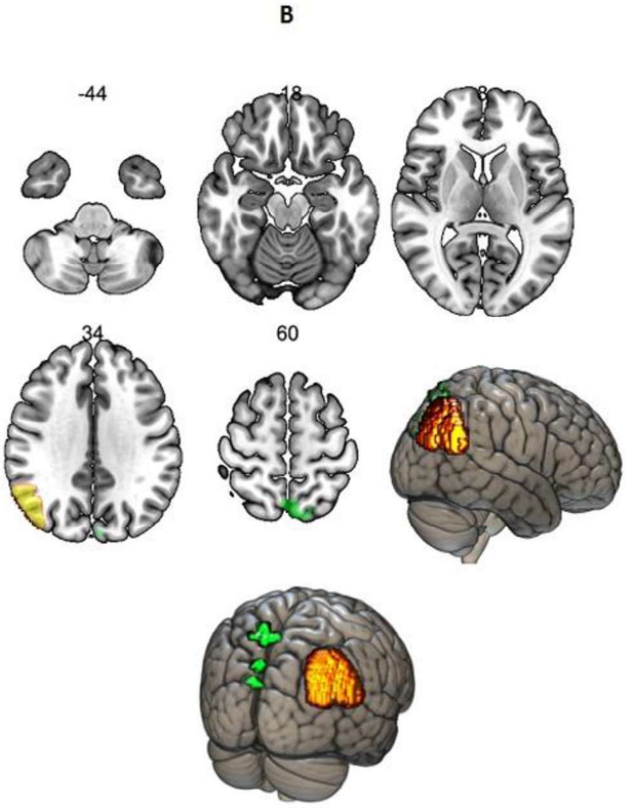
4.4.2.1 PPI results from switching to L1

Based on the masks that we created of the IPC caudal cluster the left and the right, the interaction between the psychological variable or rather the time series associated with L1 switch trials, convolved with a double gamma hemodynamic response and the physiological variable which is time series extracted from the ROI was investigated. In doing so, we looked for the functional connectivity of the ROI and the rest of the brain in the form of significant linear increases and decreases. We thresholded the Z (Gaussianised T/F) statistic images in a non-parametric manner and used the clusters that were determined by $Z > 3.1$ and a corrected cluster significance threshold of $P < 0.05$. According to our results, when participants switched to L1, there was a significant linear decrease in the functional connectivity of the left IPC caudal cluster with multiple clusters which are as follows: two clusters in the precuneus cortex, one cluster in the lateral occipital cortex, the inferior division, one cluster in the frontal pole, one cluster in the cingulate gyrus, anterior division, one cluster in the temporal occipital fusiform cortex, the posterior division, and one cluster in the lingual gyrus. The left IPC caudal cluster also showed a significant linear increase in its functional connectivity with a cluster located in the left side of the IPC in PGa (see Figure 4.2 A).

Figure 4.2

Demonstration of the seed regions, the left and the right IPC caudal clusters, and brain areas that the seed regions have functional connectivity with, when switching to L1.





Note. The yellow-red color marks the seed regions, the green color and the blue color demonstrate clusters that the seed regions have negative and positive functional connectivity with, respectively. Panel A regards the left caudal IPC and its coupling when switching to L1 and Panel B relates to the right IPC caudal cluster and its functional associations under the same experimental condition.

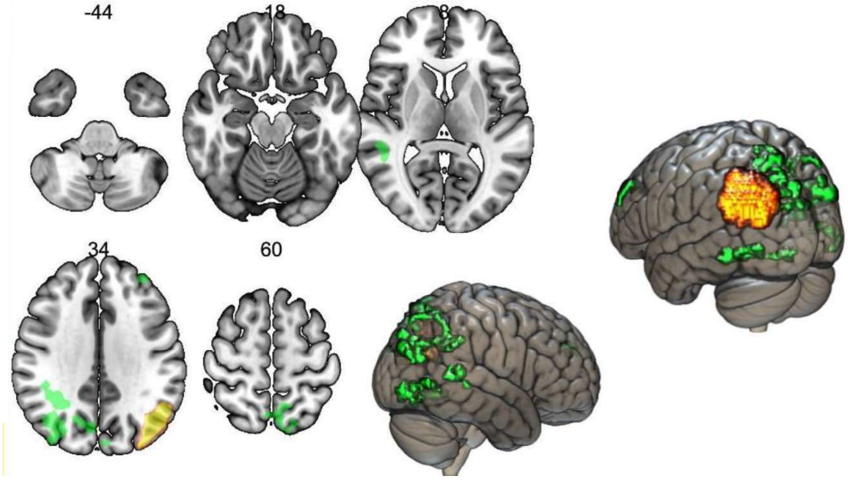
The right IPC caudal cluster showed a different pattern of functional connectivity with other parts of brain compared with the left IPC caudal cluster, when participants switched to L1. We observed a significant linear decrease in the functional connectivity between the right IPC caudal cluster and a cluster localized in the cuneal cortex; the right IPC caudal cluster did not have any positive functional association with other parts of the brain (see Figure 4.2 B and Table 4.4).

4.4.2.2 PPI results from switching to L2

When participants switched to L2, we observed a significant linear decrease in functional connectivity of the left IPC caudal cluster with two clusters localized in the lateral occipital cortex inferior division, two clusters localized in the lateral occipital cortex superior division, and one cluster localized in the frontal pole. The right IPC caudal cluster did not show any significant linear increases or decreases in functional connectivity with other parts of the brain when switching to the L2 (see Figure 4.3 and Table 4.4).

Figure 4.3

Demonstration of the seed region, the left IPC caudal cluster, and brain a reas that the seed region has functional connectivity with, when switching to L2.



Note. The yellow-red color shows the seed region and the green color demonstrate clusters that the seed region has negative functional connectivity with, when switching to L2.

Table 4.4

Clusters that the R/L IPC caudal cluster has functional connectivity with, when switching to L1/L2

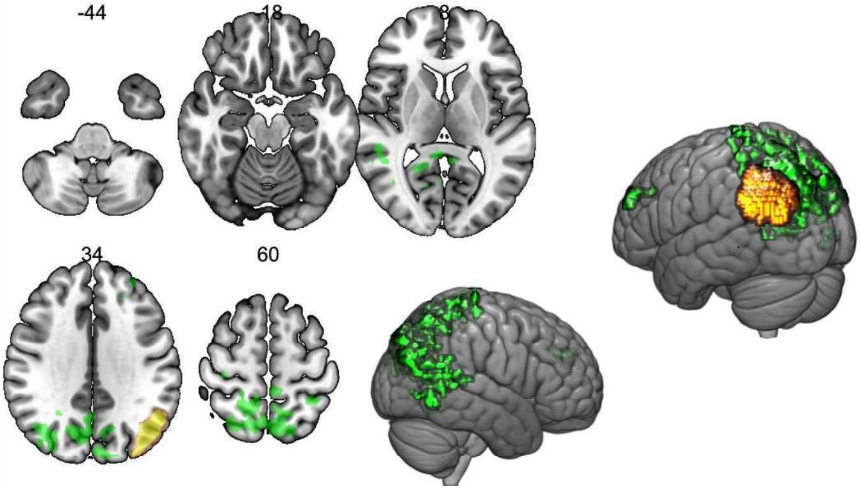
Clusters	Switch L1/L2	Voxels	Coupling	Z-Max	R/L Seed	Location (Z-COG) X Y Z
Precuneus cortex	L1	6599	Negative	5.51	L	7.25, -66.1, 43.2
Precuneus cortex	L1	421	Negative	4.32	L	14, -56.1, 9.87
Lateral occipital cortex inferior division	L1	367	Negative	4.87	L	52.3, -63.3, -3.82
Frontal pole	L1	259	Negative	5.2	L	-35.7, 46.2, 26.9
Cingulate gyrus anterior division	L1	192	Negative	4.06	L	-5.47, 31.7, 23.1
Temporal occipital fusiform posterior division	L1	153	Negative	4.01	L	29.7, -39.4, -17.2
Lingual gyrus	L1	151	Negative	4.04	L	-12.5, -60.6, 4.32
IPC caudal cluster left (PGa)	L1	129	Positive	3.92	L	-51.5, -62.7, 38.6
Cuneal cortex	L1	101	Negative	4.34	R	-3.57, -84.6, 36.1
Lateral occipital cortex inferior division	L2	305	Negative	4.68	L	-46.3, -65.3, -4.61
Lateral occipital cortex inferior division	L2	215	Negative	4.43	L	49.7, -71.4, -2.68
Lateral occipital cortex superior division	L2	242	Negative	4.43	L	-11.3, -64.3, 61.2
Lateral occipital cortex superior division	L2	140	Negative	4.06	L	-21.1, -80, 43
Frontal pole	L2	142	Negative	5.03	L	-35.1, 49.1, 29

4.4.2.3 Sensitivity analyses of PPI results from switching to L1

According to our results, when female participants switched to L1, there were a significant linear decrease in functional connectivity of the left IPC caudal cluster with four clusters; the first cluster was localized in the precuneus cortex and the second cluster was localized in the frontal pole.

Figure 4.4

Demonstration of the seed region, the left IPC caudal cluster, and brain areas that the seed region has functional connectivity with, when switching to L1 in females.



Note. The yellow-red color marks the seed region and the green color demonstrate clusters that the left IPC caudal cluster has negative functional connectivity with.

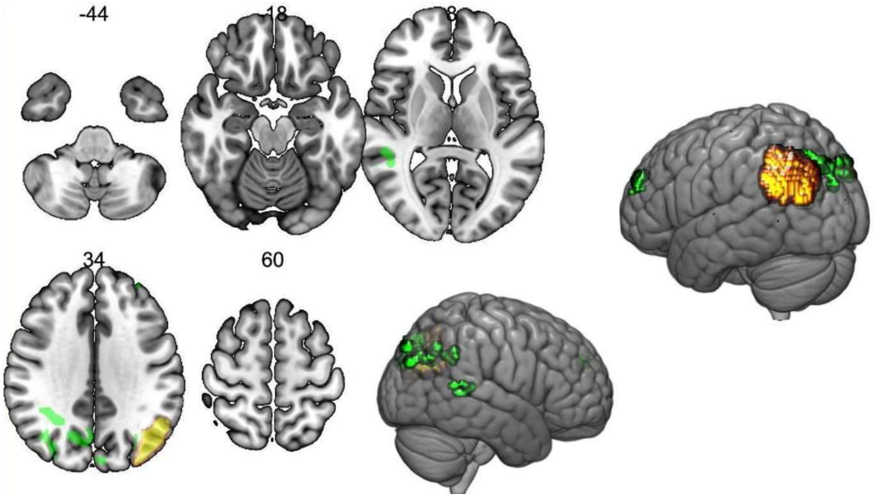
The third and the fourth cluster were localized in the lateral occipital cortex, the inferior division and in the superior partial lobule (7PCL) (see Figure 4.4). The right IPC caudal cluster did not demonstrate any significant linear increases or decreases in functional connectivity with other parts of the brain when females switched to the L1 (see Table 4.5).

4.4.2.4 Sensitivity analyses of PPI results from switching to L2

There was a significant linear decrease in the functional connectivity patterns of the left IPC caudal cluster with three clusters when female participants switched to L2. One cluster was localized in the lateral occipital cortex, superior division, and the other cluster was localized in the precuneus cortex; the third cluster was in the frontal pole (see Figure 4.5). The right IPC caudal cluster did not show any significant linear increases or decreases in functional connectivity with other parts of the brain when females switched to the L2 (see Table 4.5).

Figure 4.5

Demonstration of the seed region, the left IPC caudal cluster, and brain areas that the seed region has functional connectivity with, when switching to L2 in females



Note. The yellow-red color marks the seed region and the green color demonstrate clusters that the left IPC caudal cluster has negative functional connectivity with.

Table 4.5

Clusters that the R/L IPC caudal cluster has functional connectivity with, when females switched to L1/L2

Clusters	Switch L1/L2	Voxels	Coupling	Z-Max	R/L Seed	Location (Z-COG) X Y Z
Precuneus cortex	L1	6324	Negative	5	L	8.47, -65.4, 38.6
Frontal pole	L1	209	Negative	4.84	L	-34.4, 46, 28.3
Lateral occipital cortex inferior division	L1	138	Negative	4.16	L	54.1, -62.2, -4.39
Superior parietal lobule (7PCL)	L1	134	Negative	4	L	-33.2, -44.4, 57
Lateral occipital cortex superior division	L2	290	Negative	44	L	30.6, -79.5, 34.8
Precuneus cortex	L2	204	Negative	3.89	L	8.88, -66.1, 35.7
Frontal pole	L2	139	Negative	4.67	L	-35.8, 50, 28.1

4.5 Discussion

Using multiband EPI technique, the present study aimed to comprehensively investigate the functional connectivity patterns of the caudal IPC in a task requiring cognitive control, with two levels of cognitive demand. In doing so, we detected highly lateralized functional connectivity patterns in the caudal IPC which have both similarities and differences in the more demanding context (switching to L1) and in the less demanding context (switching to L2) that we elaborate on in the following (see Table 4.4 for a summary).

4.5.1 The highly lateralized functional connectivity of the caudal IPC

The fMRI findings showed that the functional connectivity of the caudal IPC is very lateralized, with the left caudal IPC having five functional connectivity spots in switching to L2 and eight functional connectivity areas in switching to L1 compared with only one functional connectivity area of the right caudal IPC when switching to L1. Although the higher cognitive demand involved in switching to L1 and the lower cognitive demand associated with switching to L2 have made a difference in the number of functional coupling of the caudal IPC with other parts of the brain, the cognitive demand has not played a major role in the laterality of the caudal IPC functional connectivity, with switching to L2 being entirely (left) lateralized and with switching to L1 being heavily (left) lateralized.

The lateralized function of the caudal IPC is different from the laterality difference in the rostral IPC under the same task conditions in that task demand modulates the patterns of functional connectivity of the rostral IPC with other parts of the brain. In fact, switching to L1 is characterized with bilateral recruitment of the rostral IPC, whereas switching to L2 is marked by the involvement of the right IPC rostral cluster (Tabassi Mofrad & Schiller, 2020). While the rostral IPC is well involved in cognitive control of language, we observed that the caudal IPC has no involvement in task performance under the same experimental conditions. That is, the caudal IPC is marked by its negative functional connectivity with some parts of the cortex that are active in cognitive control, in particular. Moreover, the sensitivity analyses of the PPI results from switching to L1 and to L2 similarly demonstrated the lateralized functional connectivity of the caudal IPC.

4.5.2 Similar caudal IPC functional connectivity in switching to L1 and L2

In switching to both L1 and L2, the left caudal IPC has negative functional connectivity with the frontal pole or rather the most anterior part of the prefrontal cortex. This part of the cortex is involved in processing higher-order cognitive functions (Boorman et al., 2009; Hartogsveld et al., 2018) and its interactions meets the upcoming task demands (Sakai & Passingham, 2003). Contrary to our finding, the positive functional connectivity of the prefrontal cortex and the parietal cortex in frontoparietal network and the contribution of this network to cognitive control abilities (Dosenbach et al., 2008) and adjusting and initiating cognitive control (Cole et al., 2013; Zanto & Gazzaley, 2013) have been reported in the literature. The reason is that in reporting the contribution of the IPC to cognitive control behavior, the literature has considered this part of the cortex as a whole, regardless of its tripartite organization into the rostral, the middle and the caudal clusters (Caspers et al., 2013); the literature has ignored the fact that each of the tripartite sections of the IPC has specific functional characteristics with regard to the IPC's cytoarchitectonically different areas (Caspers et al., 2013; Corbetta et al., 2008; Keysers & Gazzola, 2009).

In the current study, we have shown that in switching to both L1 and L2, the caudal IPC has negative functional connectivity with the frontal pole and that points to the fact that this is not the whole part of the IPC that contributes to cognitive control behavior in the frontoparietal network, in its traditional definition. In line with this argument, in mapping the functional associations of the rostral IPC we reported that the right side of this part of the cortex has positive functional associations with the cingulate gyrus, anterior division (Tabassi Mofrad & Schiller, 2020) when switching to L2, indicating a strong response selection circuit in that language condition, which contributes to shorter reaction times in producing L2 words in a language switching context. Thus, comparatively, while the right rostral IPC proves to be the contributing part of the IPC to cognitive control, in the frontoparietal network when switching to L2, the caudal IPC does not demonstrate to be part of a strong circuit in that network in the same language condition nor in switching to L1, in the absence of positive functional associations with other brain areas involved in cognitive control, in particular with the prefrontal cortex.

The lateral occipital cortex, the inferior division, is the other part of the cortex that in switching to both L1 and L2, the left caudal IPC has negative functional connectivity with. According to previous studies, positive functional connectivity between brain areas in the frontoparietal network and the visual regions results in better performance in cognitive abilities such as generating verbs as well as automatic word recognition (Twait & Horowitz-Kraus, 2019) and increased behavioral scores for word reading (Horowitz-Kraus & Holland, 2015). Better performance in such cognitive functions is in fact due to the increased visualization of the stimuli which via the positive functional connectivity of the visual regions with the brain areas involved in cognitive control brings about enhanced cognitive performance. In the current study, however, the negative functional associations of the left caudal IPC with the lateral occipital cortex in switching to L1 and to L2 points to the absence of the effect reported in the literature under a positive functional connectivity between brain areas involved in cognitive control and visual regions (i.e. enhanced cognitive performance) due to the deactivation of the caudal IPC in task performance.

With regard to the sensitivity analyses of the PPI results from switching to L1 and to L2, likewise the left caudal IPC has negative functional associations with both the frontal pole (as part of the frontoparietal network) and the lateral occipital cortex. Besides, when the PPI analyses are only done on the fMRI data from female participants, this is just the superior part of the lateral occipital cortex that the left caudal IPC has functional connectivity with, in switching to L2. This points to the gender-based differences in brain functional connectivity which has already been reported in the literature (Zhang et al., 2018; Zhang et al., 2020).

4.5.3 Different caudal IPC functional connectivity in switching to L1 and L2

In general, in switching to L1 which is cognitively a more demanding condition, the left caudal IPC has more negative functional associations with other parts of the brain compared with the functional connectivity patterns of the seed in switching to L2. Regarding the dissimilar patterns, when switching to L2 is concerned, the negative functional connectivity of the left caudal IPC with the lateral occipital cortex, the superior division, is prominent. However, in switching to L1, the left seed is characterized with negative functional associations with the cingulate gyrus, anterior division, the precuneus cortex, the temporal occipital fusiform, the posterior division, and the lingual gyrus. The cuneal cortex is the only part of the brain that the right caudal IPC has negative functional connectivity with in switching to L1. Besides, the only positive functional association of the caudal IPC is between the left seed and the PGa in the left caudal IPC.

We previously suggested that the co-activation of the brain areas in the frontoparietal network and the visual cortex improves some cognitive abilities (Horowitz-Kraus & Holland, 2015; Twait & Horowitz-Kraus, 2019). However, this has not been extensively addressed in the literature and thus it is not known whether the functional associations between the frontoparietal areas and different parts of the visual cortex would highlight any different behavioral effects. That is, it is not yet understood if e.g. the functional connectivity of brain areas in frontoparietal network with the lateral occipital cortex, the superior division and the lateral occipital cortex, the inferior division could differently contribute to cognitive abilities. Consequently, it cannot be concluded what different behavioral effects could be expected when such functional associations do not exist.

In the current study, when the dissimilar patterns in switching to L1 and in switching to L2 are concerned, we observed that in switching to L1, the left caudal IPC has negative functional connectivity with different parts of the visual cortex, namely, temporal occipital fusiform, the posterior division, the cuneal cortex and the lingual gyrus which are part of the occipital lobe, and in switching to L2, the left caudal IPC has negative functional connectivity with the lateral occipital cortex, the superior division. While further research is needed to map the patterns of the co-activations between brain areas involved in the frontoparietal network and different parts of the visual cortex and to address what behavioral effects would be observed, what is evident in the current study is that, in general, the more cognitively demanding context is characterized with more negative functional associations of the caudal IPC with the visual areas.

One tangible explanation is that the caudal IPC, though part of the frontoparietal network, is not part of brain areas involved in cognitive control. This further strengthens the idea that this is not the whole part of the IPC that contributes to cognitive control but one or two parts of its tripartite organization, given the fact that the IPC's cytoarchitectonically different areas as the rostral, the middle and the caudal clusters have different white matter connectivity and different functional characteristics (Caspers et al., 2013; Corbetta et al., 2008; Keysers & Gazzola, 2009).

Besides, the left caudal IPC has negative functional connectivity with the cingulate gyrus, the anterior division. Generally, this part of the cortex, as part of the language control network (Abutalebi & Green, 2008, 2016) monitors conflicts between languages and it contributes to response selection (Abutalebi et al., 2012). In mapping the functional connectivity patterns of the rostral IPC, we showed that the positive functional associations of the ACC and the right IPC rostral cluster, by forming a strong response selection circuit involved in switching to L2, contribute to shorter RTs in this context (Tabassi Mofrad & Schiller, 2020). However, the negative connectivity pattern between the IPC caudal cluster and the ACC further bolsters the idea that this part of the cortex is not involved in cognitive control.

The fact that the left caudal IPC has also negative functional associations with the precuneus cortex, which is active during the resting state (Smith et al., 2009) confirms that the caudal IPC is not related to the resting state condition either. Interestingly, clusters located in the precuneus cortex with which the left caudal IPC has negative functional connectivity, have the highest number of voxels compared with any other clusters that the left caudal IPC is negatively connected.

In switching to L1, the left caudal IPC has positive functional connectivity with the PGa which is itself part of the IPC caudal cluster. To address the general function of the angular gyrus in mental arithmetic tasks performed with Arabic and Roman numerals, Wu et al. (2009) reported that this part of the cortex was strongly deactivated in performing the task. Since the angular gyrus is identical to the caudal IPC when the correlated transmitter receptor-based organization of the IPC is concerned (Caspers et al. 2006, 2008 & 2013), our findings corroborate the research result of Wu et al. (2009) in the sense that the left caudal IPC has negative functional connectivity with the frontal pole and different parts of the visual cortex that are active during task performance, suggesting that the left caudal IPC is deactivated in performing the task. At the same time, the positive functional connectivity of the left caudal IPC with one of its own parts, namely PGa, highlights strong deactivation of PGa in switching to L1. Another interesting finding is that strong deactivation of PGa which has resulted in the positive functional association of the left caudal IPC with PGa is observed in the more demanding context and only in the left part of the cortex. However, we cannot associate the function of the caudal IPC with those of brain areas related to the resting state, as the left caudal IPC has negative functional connectivity with precuneus cortex in switching to L1.

The sensitivity analyses of the PPI results also demonstrated more negative functional associations of the left caudal IPC with other parts of the brain in the more cognitively demanding condition compared with the functional connectivity patterns of the seed in switching to L2. Moreover, the sensitivity analyses also showed the similar results for the negative functional connectivity of the seed with the lateral occipital cortex, the inferior division in switching to L1 and the negative functional connectivity of the left caudal IPC with the lateral occipital cortex, the superior division in switching to L2. While the negative functional connectivity of the left caudal IPC with the occipital cortex is preserved in the sensitivity analyses, the absence of the functional connectivity of the seed with other parts of the occipital lobe i.e. temporal occipital fusiform, the posterior division, the cuneal cortex and the lingual gyrus signals the gender-based differences in brain functional connectivity.

4.5.4 Modulating function of the caudal IPC

According to Fair et al. (2007), there is a high correspondence between parts of the cortex involved in the task-related and the resting state functional connectivity in the way that they fluctuate together (Smith et al., 2009; Cole et al., 2014); that means brain areas that are active during resting state are deactivated in doing a task, and those parts of the cortex that are active in task performance are deactivated during resting state, an example of which is the connectivity of somatosensory cortex with some parts of the cortex in the frontoparietal network (see Tabassi Mofrad & Schiller, 2019; Tabassi Mofrad, Jahn & Schiller, 2020). Thus, when in performing the language switching task, the IPC caudal cluster has negative functional connectivity with the precuneus cortex, the caudal IPC cluster cannot be associated with the resting state despite the fact that this part of the cortex has also negative functional connectivity with other parts of the brain such as different parts of the visual cortex, that are active not necessarily in cognitive control but generally in doing a task. It is noteworthy that the negative functional connectivity of the left caudal IPC with the precuneus cortex, the frontal pole and different parts the visual cortex are preserved in the sensitivity analyses of the PPI results.

Regarding our research findings, there is evidence to believe that the traditional categorization of different brain areas into either task-related, i.e. active when the brain is busy with performing a task, or resting state-related networks, i.e. active when the brain is not processing external stimuli cannot accommodate the function of caudal IPC. Thus, we hypothesize that this part of the cortex functions in a modulating manner; while it is not necessarily associated with the resting state condition - its deactivations, proportionate to task difficulty, contribute to task performance. To elaborate more, when the caudal IPC has negative association with the precuneus cortex that is the evidence that the caudal

IPC and the precuneus cortex are not fluctuating together. While the precuneus cortex is recognized as a resting-state related part of the cortex, thus, the caudal IPC is not resting-state related. Since the caudal IPC has negative connectivity with some parts of the frontoparietal network, the caudal IPC is not part of the control network. As the caudal IPC also has negative functional connectivity with parts of the cortex that are involved in very general cognitive functions e.g. different parts of the visual cortex, therefore, the caudal IPC does not show task-related activity. That is, the caudal IPC deactivations contribute to task performance; the higher the cognitive demand, the more deactivations and the more the negative functional associations. Because the number of negative functional connectivity of the caudal IPC with other parts of the cortex changes with the cognitive demand, as a result the caudal IPC has a modulating role.

Although in the current study we used a language task to map the functional connectivity of the caudal IPC, the general connectivity behavior of this part of the cortex that we have reported should not be considered as limited to a language task. For one thing, the left lateralized function of the caudal IPC is the result of the negative functional connectivity of this part of the cortex with other parts of the brain. However, the left lateral function of the brain in processing language, reported in the literature, is the result of the positive brain activations and associations. Moreover, as mentioned earlier, the general connectivity patterns of the caudal IPC correspond to neither the resting-state related nor to the task based-related parts of the cortex, by which a new brain functional category that we have referred to as modulating is hypothesized and that is highly unlikely to be task dependent.

4.6 Conclusion

For long, the functions of the IPC in cognitive control have been considered regardless of its tripartite organization into the rostral, the middle and the caudal clusters (Caspers et al., 2013). That has resulted in poor understanding of the functions of the IPC subsections and forming general characteristics for this part of the cortex which are not representative of the IPC's constituents. Mapping the functional connectivity of the caudal IPC has revealed that this brain area does not show functions that have characteristically been reported about the IPC as a whole. Besides, our research findings have demonstrated that functional associations of the caudal IPC are neither typical of resting state-related nor task-related parts of the brain. These results support the hypothesis about a modulating cortical area that its involvement in task performance, in a modulating manner, is marked by deactivation in the patterns of functional connectivity, proportionate to task difficulty, with parts of the brain that are involved in doing a task; however, its connectivity in some other respects does not correspond to the resting state-related parts of the cortex.

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Chapter 5

Connectivity profile of middle inferior parietal cortex confirms the hypothesis about modulating cortical areas

This chapter is based on:

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Abstract

According to the correlated transmitter-receptor based structure of the inferior parietal cortex (IPC), this brain area is divided into three clusters, namely, the caudal, the middle and the rostral. Nevertheless, in associating different cognitive functions to the IPC, previous studies considered this part of the cortex as a whole and thus inconsistent results have been reported. Using multiband EPI, we investigated the connectivity profile of the middle IPC while forty-five participants performed a task requiring cognitive control. The middle IPC demonstrated functional associations which do not have similarities to a contributing part in the frontoparietal network, in processing cognitive control. At the same time, this cortical area showed negative functional connectivity with both the precuneus cortex, which is resting- state related, and brain areas related to general cognitive functions. That is, the functions of the middle IPC are not accommodated by the traditional categorization of different brain areas i.e. resting state-related or task-related networks and this advanced our hypothesis about modulating cortical areas. Such brain areas are characterized by their negative functional connectivity with parts of the cortex involved in task performance, proportional to the difficulty of the task; yet, their functional associations are inconsistent with the resting state-related cortical areas.

5.1 Introduction

Based on the correlated transmitter-receptor based organization of the inferior parietal cortex (IPC), this cortical area has a tripartite structure, including the caudal, the middle and the rostral clusters (Caspers et al., 2006, 2008). The cytoarchitectonically different subareas of the IPC have also been reflected by the white matter connectivity of this part of the cortex (Caspers et al., 2013) as well as diffusion-weighted magnetic resonance imaging along with probabilistic tractography (Ruschel et al., 2014).

Despite the tripartite organization of the IPC, previous studies considered this brain area as a whole and associated the IPC with different executive functions, for instance, language control (Branzi et al., 2016), in particular language switching (Abutalebi & Green, 2008), memory functions (Martinelli et al., 2013), adaptation of behavior (Singh-Curry & Husain, 2009), attention (Tomasi & Volkow, 2011), and action observation (Apps et al., 2016). In fact, in reporting the importance of the IPC in the fronto-parietal network and the way this brain area contributes to cognitive control (Dajani & Uddin, 2015) it was ignored that the functions of the subsections of the IPC do not represent the whole IPC. The functional characteristics of the caudal, the middle and the rostral IPC are relative to their structural organization, and thus the patterns of their functional associations with other cortical areas do not constitute a unified representation of the IPC.

Until the time we reported the functional connectivity profiles of the rostral and the caudal IPC in a task which required cognitive control (Tabassi Mofrad & Schiller, 2020; 2022), in previous studies the functional associations of the clusters of the IPC with other parts of the brain had never been investigated. Examining the fiber tracks between the IPC's subareas and other parts of the cortex has made it clear that while the rostral IPC has connectivity with the motor, the inferior frontal, the somatosensory and the premotor areas, the caudal IPC has strong associations with the temporal, the visual and the posterior parietal areas. The middle IPC, however, has similarity with the caudal and the rostral IPC, in terms of white matter connectivity, by being associated with the intraparietal, the superior and the frontal areas (Caspers et al., 2011). Nonetheless, the fiber tracks reflect brain white matter connectivity, and they do not necessarily point to brain functional connectivity. That is, at the same time that cytoarchitectonically different subareas of the IPC have been differentiated and their fiber tracks have been detected, the functional connectivity profile of the middle IPC has yet remained a gap in the literature. According to the traditional definition of the IPC, this brain area is believed to process cognitive control; however, when the subareas of the IPC are concerned, the contribution of the middle IPC to cognitive control is still unknown.

In our previous study (Tabassi Mofrad & Schiller, 2020), we elaborated on the functions of the rostral IPC; this brain area, by having positive functional associations with the anterior cingulate cortex, is the contributing part of the IPC in the frontoparietal network to cognitive control. Besides, the rostral IPC forms a strong response selection circuit in cognitive control of language. However, the caudal IPC has different functional connectivity patterns and dissimilar functions to those of the rostral IPC. Mapping the connectivity profile of the caudal IPC demonstrated that this part of the brain does not contribute to cognitive control and its connectivity patterns are neither typical of the task-related nor the resting state-related brain areas - according to which we proposed the hypothesis about modulating cortical areas (Tabassi Mofrad & Schiller, 2022). By that hypothesis we delineated that the involvement of the modulating cortical areas in task performance is characterized by negative functional connectivity with task-related brain areas, proportional to task difficulty. At the same time, functional associations of the modulating cortical areas are not similar to those of the resting state-related parts of the cortex.

Having mapped the functional connectivity of the caudal and the rostral IPC in doing a task which required cognitive control, as part of our wide-ranging project to map the functional associations of the clusters of the IPC, in this study we addressed the functional connectivity profile of the middle IPC mostly via an exploratory approach, as to the knowledge of the researchers, the functional associations of the middle IPC are not reported in previous studies – according to which a logical hypothesis could be formed. Having said that, we expected that the patterns of functional connectivity that the middle IPC would demonstrate might be dissimilar to the general functional couplings of the IPC as a whole, when task involvement is concerned, due to structural differences of the clusters of the IPC. In mapping the functional connectivity profile of the middle IPC, we used multiband EPI (factor = 4). This technique provided us with one of the fastest repetition times (TR = 690 ms) in MRI image acquisition, which resulted in increased sensitivity in detecting functional associations of cortical areas (Liao et al., 2013; Preibisch et al., 2015), increased sensitivity of BOLD acquisition (Kundu et al., 2012), and increased temporal and spatial resolution (Chen et al., 2015).

5.2 Methods

5.2.1 Participants

Bilingual Dutch-English psychology students at Leiden University (fifty-two volunteers, healthy, aged 18-27, right-handed, with corrected-to-normal or normal vision) took part in this study. Due to excessive movements in the scanner (movement exceeding ~1–2 mm; see Wylie et al., 2014), we did not include the data from seven participants in the analyses. Thus 34 females and 11 males remained in the final set of participants. Participants were well informed about all stages of the experiment, and they submitted their consent to take part in this research. Participants received either course credits or a small financial compensation for their participation. The medical ethics committee of the Leiden University Medical Center (Leiden, The Netherlands) approved the research protocol (application no. NL61816.058.17).

5.2.2 Stimuli

The stimuli included 48 pictures taken from the International Picture Naming Project (IPNP). In selecting the pictures, we considered some variables in both Dutch and English which are as follows: H statistics, onset sound, number of letters and syllables, RT (mean) and word complexity; both the IPNP and CELEX lexical database were used as references. Moreover, we also considered word frequency, conceptual complexity, and visual complexity to make two sets of twenty-four stimuli – set A and set B – that were parallel and counterbalanced across participants.

5.2.3 Procedure

Participants performed a language-switching experiment which was controlled by the E-Prime software. The experiment had four conditions and they switched between English (L2) and Dutch (L1). Trials were either switch ones - the language in the preceding trial was different from the language in the following trial - or non-switch trials, that is, the language in the preceding trial and the following trial was the same. The fMRI experiment was event-related and consisted of one run of 6 min and 46s. Each trial began with a visual cue - a blue or red frame - for 250 ms, which was counterbalanced. The visual cue instructed the participant whether to use Dutch or English to name the demonstrated picture in that trial. The visual cue was followed by a fixation cross and the presentation of a picture, for 500 ms and 2,010 ms, respectively. There was a jittered blank screen with a duration varying between 690 and 2,760 ms, at the end of each trial; the presentation of trials was pseudo-randomized. Before conducting the experiment inside the MRI scanner, participants took part in a small scale of the task to familiarize them with the pictures that we used in the experiment. That also facilitated learning the association between the target language and the color cue. Participants were instructed to move their jaws minimally when naming the target pictures to avoid movement related artifacts.

5.2.4 fMRI data acquisition

The neuroimaging data were acquired in the Leiden University Medical Center, using a 3 Tesla Philips Achieva TX MRI scanner which was equipped with a SENSE-32 channel head coil. First the high-resolution anatomical images were acquired including a 3D gradient-echo T1-weighted sequence with the following parameters: TR = 7.9 ms, TE = 3.5 ms, FA = 8°, FOV = 250 x 195.83 x 170.5 mm3, 155 slices 1.1×1.1×1.1 mm3. Then 555 T2*-weighted whole brain multiband gradient EPIs were collected with the following scanning parameters: TR = 690 ms, TE = 30 ms, multiband factor = 4, FA = 55°, FOV = 220 x 220 x 121 mm3, 44 slices 2.75 × 2.75 × 2.75 mm3. A high-quality MRI-safe HD 32" LCD monitor was located at the end of the scanner for displaying the visual stimuli. Participants viewed the stimuli through a mirror which was attached to the head coil.

5.3 Data analysis

5.3.1 Behavioral data analysis

SPSS software version 23 was used to process the behavioral data which were the reaction time (RT) in doing the language switching experiment. A two (language: English vs. Dutch) by two (context: non-switch vs. switch) repeated-measures ANOVA was used to examine the effects of language and context. Then paired t-tests were done to examine whether RTs in L1 and L2 switch trials were statistically different.

5.3.2 Pre-processing of fMRI data

FSL software version 5.0.10 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) was used to analyze the fMRI data with the following pre-statistics processing: spatial smoothing (Gaussian kernel of FWHM 5 mm), motion correction by using MCFLIRT (Jenkinson et al., 2002), non-brain removal by using BET (Smith, 2002), high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma

= 50.0s) and grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor. The functional images were registered to the MNI-152 standard space. The registration was done using a three-step procedure i.e. functional to high-resolution images, then to T1-weighted structural images, and finally to the standard space of the MNI template, using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002).

5.3.3 Psychophysiological interaction (PPI) analysis

PPI analyses were conducted to analyze the functional connectivity of the middle IPC with other cortical areas. Using the Jülich Histological Atlas, masks of the right and the left middle IPC were created. The probabilistic maps of the left and the right IPC middle cluster were binarised and then thresholded at 50 percent, before transforming them into the functional space. The ROI was projected on the functional images that were already pre-processed, and by using fslmeants, the mean time series from the ROI was extracted. For the right and left IPC middle clusters, separate PPI analyses were carried out by using FEAT (FMRI Expert Analysis Tool) version 6.00. The design matrix had three regressors which are as follows: the physiological variable i.e. the time series that were extracted from the ROI, the psychological variable, convolved with a double gamma hemodynamic response, and the interaction between the physiological and the psychological variables (PPI). The significant linear increases and decreases in functional couplings of the right and left middle IPC with other cortical areas when participants did the language switching experiment were the main focus of the PPI analyses. To correct for multiple comparisons, cluster correction was employed as the most popular correction method in fMRI data analysis (see Woo et al., 2014). The cluster-defining threshold was set by considering a z-value of 3.1.

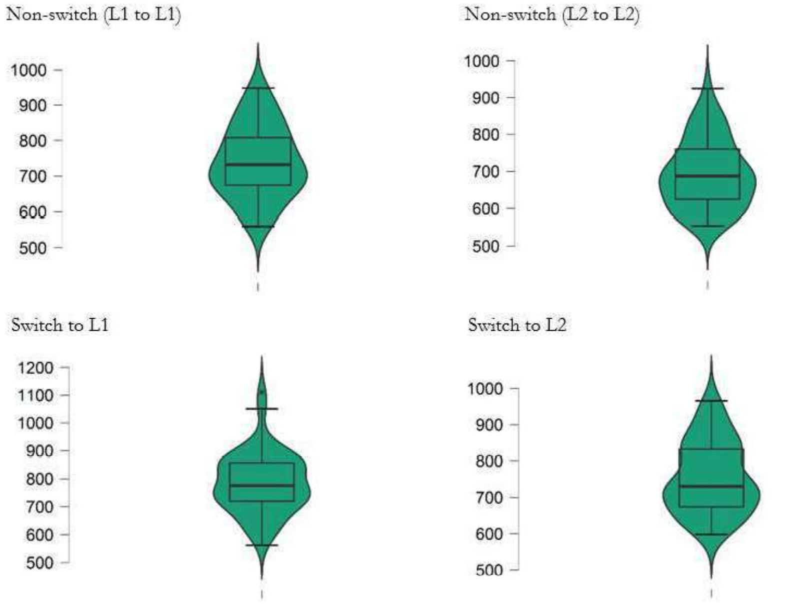
5.4 Results

5.4.1 Behavioral data

Results from repeated-measures ANOVA revealed a significant main effect for context ($F1(1, 44) = 75.63$, $P < 0.0001$, partial eta square = 0.63) as well as language ($F1(1, 44) = 48.53$, $P < 0.0001$, partial eta square = 0.52). However, we did not observe any interaction between context and language ($F1(1, 44) = 3.7$, $P = 0.061$, partial eta square = 0.07).

Figure 5.1

Visualization of the distribution of the behavioral results (in RTs) in all four conditions of the experiment.



Note. In both contexts, L2 lexical production was faster than that of L1.

In order for the bilinguals to speak in the non-dominant language (L2), the dominant language (L1) is suppressed, and because retrieving the language that is more inhibited is also more demanding (Green, 1998) the stronger language has longer RTs in both non-switch and switch trials; hence, the reversed language effect (Christoffels et al., 2016; Ghafar Samar et al., 2014; Tabassi Mofrad et al., 2015; 2017). According to the results from the paired t-test, switching to the L1 was significantly slower than switching to the L2 (t1(44) = -3.859, L1 Mean RT = 784.25, L2 Mean RT = 754.32, P < 0.0001; t2(47) = -3.326, P < 0.002) (see Figure 5.1). Thus, that underlines the fact that in language-switching, retrieving items from the lexicon of the more dominant language is cognitively more demanding.

5.4.2 PPI results

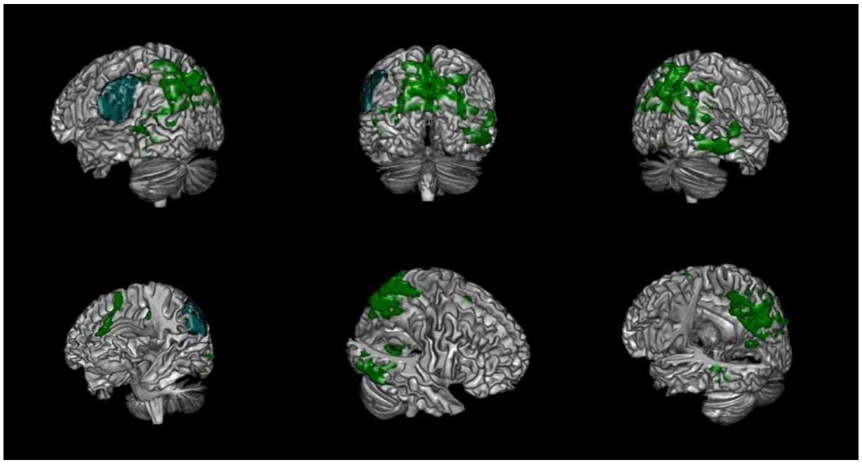
5.4.2.1 PPI results from switching to L1

The interaction between the time series related to L1 switch trials or rather the psychological variable, and the physiological variable was investigated using the masks created of the right and the left middle IPC. The Z (Gaussianised T/F) statistic images were thresholded in a non-parametric way, and we used clusters that were determined by Z>3.1. We investigated the functional association of the ROI with other cortical areas by considering significant linear decreases and increases. Based on our results, when switching to L1, there was significant linear decrease in the functional association between the left middle IPC and some other clusters, namely, two clusters in the lateral occipital cortex inferior division, one cluster in the precuneus cortex, one cluster in the cingulate gyrus, anterior division, one cluster in the lingual gyrus and one cluster in the occipital fusiform gyrus (see Figure 5.2 Panel A).

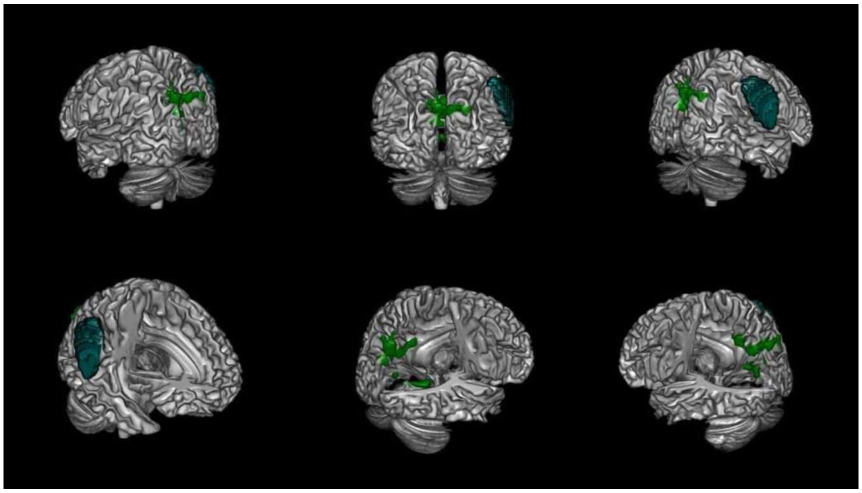
Figure 5.2

Demonstration of the seed regions, the left and the right IPC middle clusters, and brain areas that the seed regions had functional connectivity with, when switching to L1.

Panel A



Panel B



Note. The seed region is marked by the cyan color and the green color demonstrates clusters that the seed regions had negative functional connectivity with. Panel A regards the left middle IPC and its coupling when switching to L1 and Panel B relates to the right IPC middle cluster and its functional associations under the same experimental conditions.

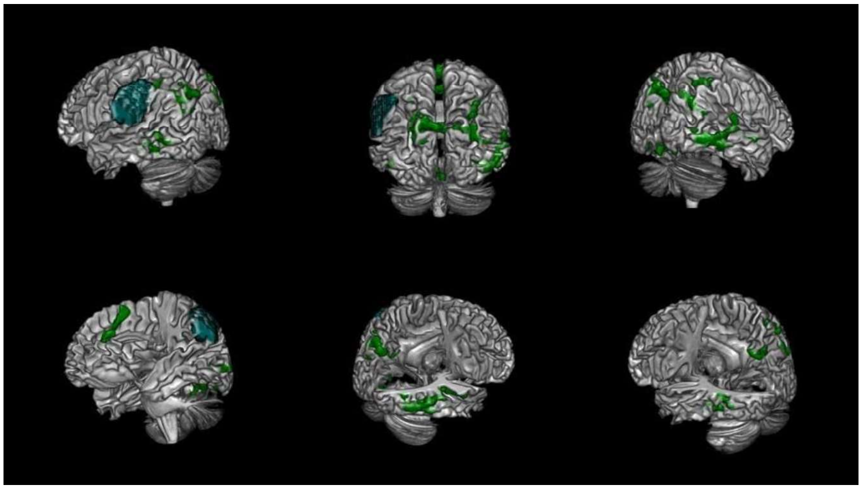
Besides, the right middle IPC demonstrated negative functional connectivity with two clusters, one in the precuneus cortex and the other in the intracalcarine cortex (see Figure 5.2 Panel B). In switching to the L1, left and right middle IPC did not show any positive functional connectivity with other cortical areas.

5.4.2.2 PPI results from switching to L2

When switching to the L2, the left middle IPC had negative functional coupling with multiple clusters in the lateral occipital cortex, inferior and superior divisions, the cingulate gyrus, anterior division and the paracingulate gyrus. The left middle IPC did not show any positive functional connectivity with other cortical areas. In addition, the right middle IPC did not demonstrate any positive or negative associations with other cortical areas either, when participants switched to the L2 (see Figure 5.3).

Figure 5.3

Demonstration of the seed region, the left IPC middle cluster, and brain areas that the seed region had functional connectivity with, when switching to L2.



Note. The cyan color demonstrates the seed region, and the green color shows clusters that the seed region had negative functional connectivity with, when participants switched to the L2.

Table 5.1

Clusters that the R/L IPC middle cluster has functional connectivity with, when switching to the L1/L2

Clusters	Switch L1/L2	Voxels	Coupling	Z-Max	R/L Seed	Location (Z-COG) X Y Z
Precuneus cortex	L1	5949	Negative	5.67	L	1.93, -68.9, 42.4
Lateral occipital cortex inferior division	L1	924	Negative	4.96	L	50.4, -62.5, -2.51
Lateral occipital cortex inferior division	L1	207	Negative	4.17	L	-45.9, -69, 4.92
Cingulate gyrus anterior division	L1	318	Negative	4.24	L	-1.83, 31.9, 23.1
Occipital fusiform gyrus	L1	226	Negative	4.34	L	-26.5, -66, -11.6
Lingual gyrus	L1	104	Negative	4	L	19.5, -57.4, 3.66
Precuneus cortex	L1	797	Negative	4.43	R	3.81, -71.6, 38.4
Intracalcarine cortex	L1	181	Negative	4.42	R	15.7, -62.7, 7.35
Lateral occipital cortex inferior division	L2	717	Negative	4.66	L	49, -64.2, -2.42
Lateral occipital cortex superior division	L2	549	Negative	4.75	L	31.8, -67.7, 38.9
Paracingulate gyrus	L2	268	Negative	4.58	L	2.35, 13.5, 50.5
Cingulate gyrus anterior division	L2	150	Negative	4.26	L	3.6, 29.3, 27.3

5.5 Discussion

Despite the cytoarchitectonically tripartite structure of the IPC into the caudal, the middle and the rostral clusters (Caspers et al., 2013), by considering general characteristics for this part of the brain, for years the IPC was believed to be a cognitive control area while the functions of the subsections of this cortical area are not representative of the whole IPC. In this study we addressed the connectivity profile of the middle IPC in the context of a task requiring cognitive control, characterized by two different levels of cognitive demand – with switching to the L1 being cognitively more demanding compared with switching to the L2. The results (see Table 5.1 for a summary) advanced our hypothesis about the modulating cortical areas (Tabassi Mofrad & Schiller, 2022); such brain areas are characterized by negative functional connectivity with cortical areas that are involved in task performance proportional to task difficulty. Yet, their patterns of functional associations in some other respects are not similar to the resting state-related parts of the brain. Thus, considering brain areas as either task-related or resting-state related cannot explain the functions of the modulating cortical areas.

Like the connectivity profile of the caudal IPC (Tabassi Mofrad & Schiller, 2022), the middle IPC demonstrated highly lateralized negative functional couplings with the cingulate gyrus anterior division in the cognitive control network, multiple parts of the visual cortex as well as the precuneus cortex, when participants performed the experiment. A negative functional connectivity refers to a negative Pearson cross-correlation coefficient between two brain areas (see Chen et al., 2011). According to our research findings, the number of the functional connectivity of the middle IPC with other cortical areas is affected by the level of cognitive demand since under the condition requiring a higher level of cognitive control (switching to the L1) the middle IPC had more functional connectivity with other cortical areas. However, the lateral functional association of this brain area remains independent of the cognitive demand as switching to the L1 is heavily (left) lateralized and switching to the L2 is entirely (left) lateralized.

As mentioned above, the cingulate gyrus anterior division is one of brain areas that regardless of the level of cognitive demand, the middle IPC has negative functional coupling with. In general, the cingulate gyrus anterior division is implicated in attention (Aarts & Roelofs, 2010), error prediction (Silvetti et al., 2013), task monitoring (Khamassi et al., 2015), anticipation of effort and reward in cognitive tasks (Vassena et al., 2014) and decision-making (Klein-Flügge et al., 2016; Shenhav et al., 2016). Besides, for long, the interplay of the IPC in its traditional definition and the ACC as part of the frontoparietal network has been reported in the literature, for example in flexibility, inhibition, working memory (Yarkoni et al., 2005), and during action observation (Apps et al., 2016). However, in investigating the involvement of the IPC in different executive functions and even the interaction of this cortical area with the ACC, previous studies considered the IPC as a whole while the tripartite structure of the IPC based on the correlated transmitter-receptor based organization of this brain area, into the caudal, the middle and the rostral clusters have clarified specific functional characteristics for the sub-divisions of the IPC (Corbetta et al., 2008; Caspers et al., 2013; Keysers & Gazzola, 2009). In fact, this is not the whole part of the IPC, but only the rostral IPC, that via positive functional coupling with the ACC and forming a strong circuit in the frontoparietal network, is involved in cognitive control (Tabassi Mofrad & Schiller, 2020). Nevertheless, the negative functional association of both the caudal IPC (Tabassi Mofrad & Schiller, 2022) and the middle IPC with the ACC, according to the current research results, prove lack of involvement for these two clusters of the IPC in the cognitive control network; both the middle and the caudal IPC have entirely dissimilar functions compared with those of the rostral IPC.

The middle IPC also showed negative functional association with the paracingulate gyrus which is in the medial prefrontal cortex. This cortical area is generally involved in attention, working, spatial or long-term memory (see Jobson et al., 2021), decision making (Euston et al., 2012) and cognitive control (Kragel et al., 2018). The negative functional coupling of the middle IPC with the paracingulate gyrus forms additional evidence for the fact that the middle IPC has no contribution to cognitive control.

In our study, the negative functional connectivity of the middle IPC with multiple parts of the visual cortex i.e. the lateral occipital cortex, the inferior and the posterior divisions, the occipital fusiform gyrus, the lingual gyrus, and the intracalcarine cortex – also demonstrated that this cortical area is not involved in general cognitive functions. Based on previous studies, positive functional association between the visual cortex and cortical areas in the frontoparietal network contributes to improved performance in tasks requiring cognitive abilities, for instance reading words (Horowitz-Kraus & Holland, 2015), in addition to word recognition and generating verbs (Twait & Horowitz-Kraus, 2019). Enhanced performance in the aforementioned cognitive functions, because of the positive functional association between parts of the cortex involved in cognitive control and visual regions, is believed to be the result of better visualization of the stimuli and hence the enhanced cognitive performance. However, the negative functional association of the middle IPC with different parts of the visual cortex, when participants did the experiment suggests deactivation of this part of cortex when cognitive control was required.

The deactivation in the functional connectivity of the middle IPC with brain areas involved in both cognitive control and general cognitive functions can feed the idea that this part of the cortex is resting state-related, however, our research results demonstrated that the functions of the middle IPC do not fit into that category either. As mentioned earlier, the middle IPC has negative functional association with the precuneus cortex. As reported by Fair et al. (2007), there is a high correlation between cortical areas which are involved in brain resting-state functional connectivity in the sense that they fluctuate together. In general, cortical areas which are active during the resting-state demonstrate negative activation when conducting a task, and those brain areas that are active when doing a task show negative activation during the resting-state condition, of which the functional connectivity of the somatosensory cortex with some brain areas involved in the frontoparietal network is an example (see Tabassi Mofrad & Schiller, 2019; Tabassi Mofrad et al., 2020). Since the middle IPC showed negative functional connectivity with the precuneus cortex, which is active during the resting-state, the middle IPC cannot be considered a resting state-related part of the cortex.

In detecting the connectivity profile of the caudal IPC, we reported that this cortical area does not fit into the classic categorization of brain areas as task-related, i.e., parts of the cortex that show activities related to task performance, and resting state-related, i.e. brain areas that are active in the absence of processing any external stimuli - according to which we proposed the hypothesis about modulating cortical areas (Tabassi Mofrad & Schiller, 2022). While the connectivity patterns of the rostral IPC demonstrated that this brain area in the frontoparietal network is involved in cognitive control functions (Tabassi Mofrad & Schiller, 2020), the middle IPC showed similar connectivity patterns to those of the caudal IPC.

Investigating the connectivity profile of the middle IPC has demonstrated that this part of the cortex also has distinctive connectivity patterns with other cortical areas in a modulating manner, characterized by deactivations in its functional associations, proportional to the difficulty of the task. This is in fact the negative functional connectivity of the modulating cortical areas with other parts of the cortex that contributes to task performance. The more demanding the task is, the more negative functional associations of the modulating cortical areas, in particular, with parts of the cortex in the visual region and in the cognitive control network/frontoparietal network would be observed. However, the functional connectivity patterns of the middle IPC, by having negative functional associations also with the precuneus cortex, revealed that this part of the brain is not resting state-related. This advanced our hypothesis about modulating cortical areas (Tabassi Mofrad & Schiller, 2022), the characteristics of which are not accommodated by the classic categorization of brain areas.

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Chapter 6

Distinct connectivity patterns in clusters of inferior parietal cortex

This chapter is based on:

Tabassi Mofrad, F., & Schiller, N. O. (under review). Distinct connectivity patterns in clusters of inferior parietal cortex.

Abstract

The inferior parietal cortex (IPC) is a complex brain region with the rostral, the middle and the caudal clusters, and functionally connected to several other cortical areas. Various cognitive functions are suggested to be governed by the IPC, however, due to ignoring the tripartite structure of this part of the brain, contradictory research reports abound in the literature. Here, we address the functional connectivity behaviour of the clusters of the IPC and point out that only the rostral cluster of this parietal area is involved in cognitive control and not the whole IPC. We also explicate the unique connectivity profiles of the middle and the caudal clusters of this part of the cortex which are not accommodated by the traditional classification of brain areas as either being task-based or being related to the resting-state functionality of the brain. The middle and the caudal IPC demonstrate negative functional associations with cortical areas involved in general cognitive functions, executive functions, in addition to the precuneus cortex, proportional to cognitive demand, in a modulating manner.

6.1 Introduction

The inferior parietal cortex (IPC) is usually known as being involved in executive functions, such as attention, memory, and processing language (Bareham et al., 2018; Buchsbaum & D'Esposito, 2011; Bzdok et al., 2016). However, such roles for the IPC are contrasted with some other research findings that consider this cortical area part of the default mode network (Doose et al., 2020; Mars et al., 2012; Raichle, 2015) - which decreases its activity when our brain is focused on explicit tasks (Smallwood et al., 2021) – and such contradictory findings about the functions of the IPC have remained in the literature for years.

According to the structural properties of the IPC, this part of the brain consists of three clusters, namely, the rostral, the middle and the caudal (Caspers et al., 2006; 2008). However, in investigating the functions of the IPC, previous research considered this part of the cortex as a whole, regardless of the fact that each cluster of the IPC has a different transmitter receptor-based organization and thus they might have different functions. Research on the white matter connectivity of the IPC in addition to the diffusion-weighted magnetic resonance imaging also point to the cytoarchitectonically different areas of the IPC (Caspers et al., 2013; Ruschel et al., 2014).) reflected by its clusters. Yet, until the time we mapped the functional connectivity of the clusters of the IPC, no studies had investigated the contribution of the rostral, the middle and the caudal IPC to cognitive control in a comparative manner, while that could have addressed the contradicting reports on how IPC functions.

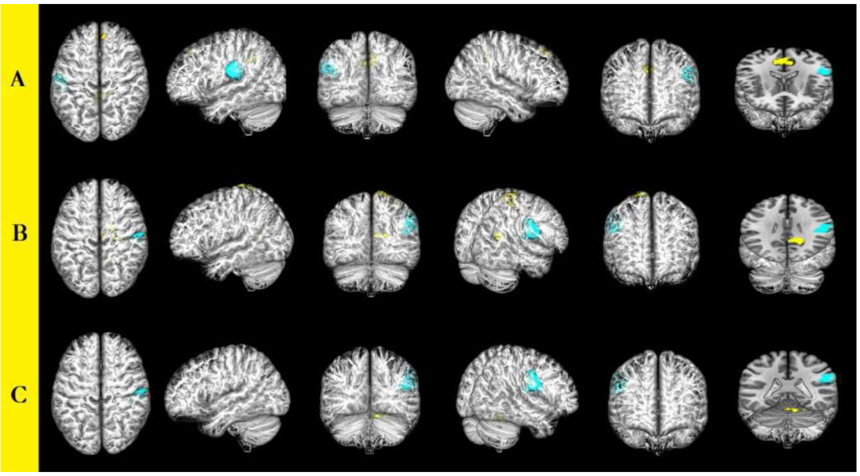
Based on the idea that the functional characteristics of the sub-regions of the IPC are underlined by their structural organization and given the inconsistent nature of research findings regarding the IPC, under the same experimental conditions we investigated the functional connectivity profiles of the clusters of this cortical area in a task which required cognitive control, with two different levels of cognitive demand. In this perspective, research findings from our comprehensive project in map the functional connectivity of the clusters of the IPC are presented and discussed, starting with the contribution of the rostral IPC to cognitive control, followed by unique connectivity profiles of the caudal and the middle IPC. The objectives are to highlight the fact that this is only the rostral IPC that contributes to cognitive control in the frontoparietal network (FPN) - not the whole IPC - and to emphasize that the connectivity patterns of the middle and the caudal IPC characteise these two parietal areas with distinctive features which are unaccommodated by traditional categorization of brain areas as either being involved in task performance or being related to the resting-state functionality of the brain.

6.2 Contributions of rostral IPC to cognitive control

The rostral IPC is the only cluster of this cortical area that is involved in cognitive control. Under the more demanding context of cognitive control, the rostral IPC has negative functional couplings with the superior frontal gyrus, the postcentral gyrus, and positive association with the cerebellum (the posterior lobe, the declive). Regarding the postcentral gyrus, the location of the primary somatosensory cortex, previous studies reported positive functional connectivity between this brain area and the FPN in individuals with better performance in executive functions during resting state fMRI (Reineberg et al., 2015). However, since we used task-based fMRI, the decreased functional connectivity between the rostral IPC and the superior frontal gyrus contributes to cognitive control. Besides, the cerebellum is known to contribute to higher order cognitive functions (Bellebaum & Daum, 2007), in addition to being part of the language control network (Green & Abutalebi, 2013; Krienen & Buckner, 2009). Thus, the positive functional connectivity of the rostral IPC and the cerebellum corroborates previous findings of the involvement of these two brain areas in cognitive control (see Figure 6.1).

Figure 6.1

Demonstration of brain areas that the rostral IPC is functionally connected with, in the more demanding context.

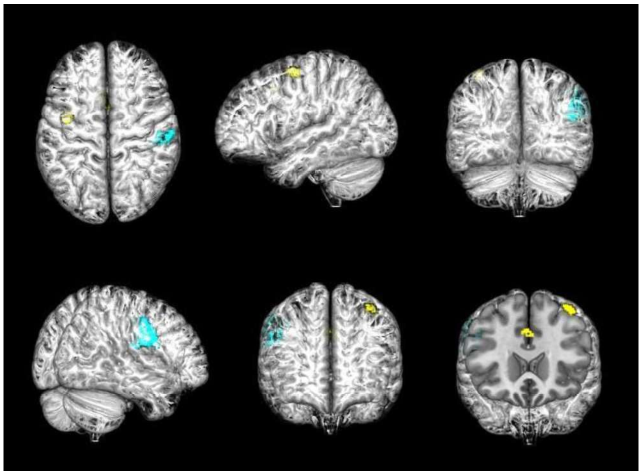


Note. The yellow color demonstrates brain areas that the rostral IPC (shown in cyan) is functionally connected with, in the more demanding context of cognitive control. The descriptions of each row are as follows: A) negative functional connectivity of the left rostral IPC with the superior frontal gyrus and the precuneus cortex, B) negative functional connectivity of the right rostral IPC with the postcentral gyrus and the precuneus cortex, C) positive functional connectivity of the right rostral IPC with the posterior lobe of the cerebellum.

Under the same experimental conditions, both the right and the left rostral IPC have negative functional connectivity with the precuneus cortex. When brain processes external stimuli, the precuneus cortex reduces its activity relative to the degree of the difficulty of the task. That is, the more difficult the task is, the more negative activity of the precuneus cortex would be observed (Dang, O'Neil & Jagust, 2013); hence, the reason the rostral IPC, as a task-related cortical area, demonstrate negative functional connectivity with this part of the brain.

Figure 6.2

Demonstration of brain areas that the rostral IPC is functionally connected with, in the less demanding context.



Note. The yellow color demonstrates brain areas (the precentral gyrus and the anterior division of the cingulate gyrus) that the right rostral IPC (shown in cyan) has positive functional connectivity with, in the less demanding context of cognitive control.

Regarding the less demanding context of the cognitive control, the right rostral IPC has positive functional connectivity with the anterior cingulate cortex (ACC) and the precentral gyrus. The ACC, as part of the control network (Abutalebi & Green, 2008, 2016), is involved in e.g. speech monitoring (Christoffels, Formisano, & Schiller, 2007) and monitoring the conflict between languages (Abutalebi et al., 2012). Therefore, the positive coupling of the rostral IPC and the ACC, by forming a strong circuit results in better task performance. Moreover, our findings elucidated that the connectivity of the rostral IPC with the precentral gyrus brings about a facilitatory function in cognitive control (see Figure 6.2).

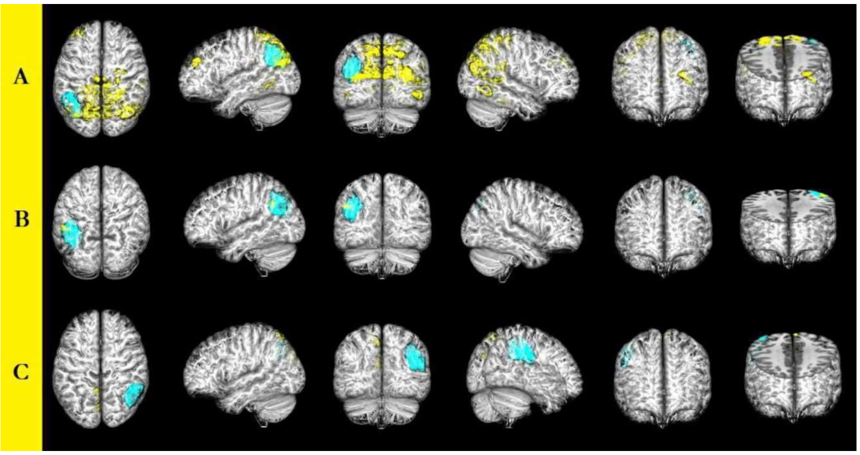
6.3 Unique connectivity profile of caudal IPC

The caudal IPC, however, is characterized with entirely different connectivity patterns from those of the rostral IPC. In fact, this part of the cortex has no similarity to a cognitive control area (Tabassi Mofrad & Schiller, 2022), in particular by having negative functional connectivity with the ACC (Tabassi Mofrad & Schiller, 2020) which is heavily involved in processing cognitive control (Braem et al., 2017; Brockett et al., 2020). Besides, regardless of degree of the cognitive demand, the left caudal IPC has negative coupling with the frontal pole, the anterior part of the prefrontal cortex, which contributes to cognitive control (Hartogsveld et al., 2018; Menon et al., 2022; Zanto & Gazzaley, 2013); such negative functional associations of the caudal IPC with cognitive control-related parts of the cortex evidence that the caudal IPC is not involved in processing cognitive control in the FPN (see Figures 6.3 & 6.4).

The caudal IPC also has negative functional connectivity with different parts of the visual cortex when the task requires cognitive control. In comparison, under the more demanding context of the cognitive control, the caudal IPC demonstrates negative functional connectivity with the fusiform gyrus, posterior division, the cuneal cortex, the lateral occipital cortex, the inferior division, and the lingual gyrus; under the less demanding context of the cognitive control, the caudal IPC has negative functional connectivity with the lateral occipital cortex, the superior division (Tabassi Mofrad & Schiller, 2022). Thus, more cognitive demand results in more negative functional connectivity of the caudal IPC with different parts of the visual cortex.

Figure 6.3

Demonstration of brain areas that the caudal IPC is functionally connected with, in the more demanding context.

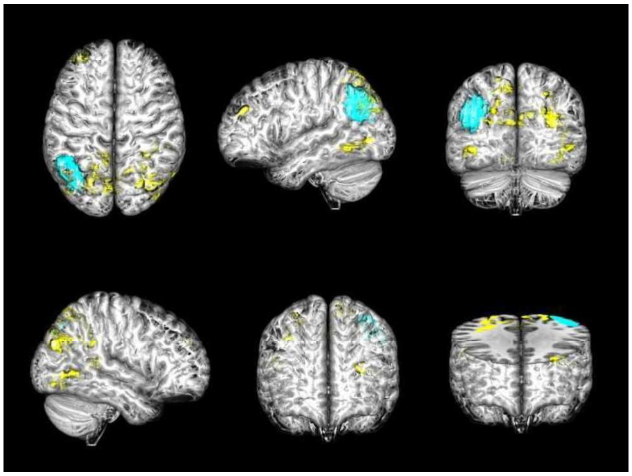


*Note***.** The yellow color demonstrates brain areas that the caudal IPC (shown in cyan) is functionally connected with, in the more demanding context of cognitive control. The descriptions of each row are as follows: A) negative functional connectivity of the left caudal IPC with the precuneus cortex, the inferior and posterior divisions of the lateral occipital cortex, the frontal pole, the anterior division of the cingulate gyrus, the posterior division of the temporal occipital fusiform and the lingual gyrus, B) positive functional connectivity of the left caudal IPC with the IPC caudal cluster left (PGa), C) negative functional connectivity of the right caudal IPC with the cuneal cortex.

While positive coupling between brain areas in the FPN and the visual cortex would result in better cognitive abilities such as word recognition (Twait & Horowitz-Kraus, 2019) and reading (Horowitz-Kraus & Holland, 2015), lack of a positive fluctuation between the caudal IPC and different parts of the visual cortex - the type of functional connectivity which is dissimilar to those of cognitive control related parts of the brain - demonstrates that this parietal area is not involved in other cognitive functions either.

Figure 6.4

Demonstration of brain areas that the caudal IPC is functionally connected with, in the less demanding context



Note. The yellow color demonstrates brain areas (the inferior and posterior divisions of the lateral occipital cortex and the frontal pole) that the left caudal IPC (shown in cyan) has negative functional connectivity with, in the less demanding context of cognitive control.

Our research findings also revealed that the caudal IPC has negative functional association with the precuneus cortex which is active when brain is not processing external stimuli. Taking into account that cortical areas that are involved in task performance decrease activity during the resting state, and those parts of the cortex that are active in the absence of external stimuli decrease activity when doing a task, the negative functional connectivity of the caudal IPC with the precuneus cortex indicates that this parietal area is not resting state related. Likewise, the negative couplings of the caudal IPC with cognitive control areas evidence that this part of the cortex does not contribute to cognitive control in the FPN. Furthermore, the negative functional connectivity of the caudal IPC with different parts of the visual cortex demonstrates that this brain area is not involved in general cognitive functions. Thus, the caudal IPC is not a task-related part of the brain.

Having negative connectivity patterns with both the resting state and the task based-related cortical areas characterize the caudal IPC with distinctive features, highlighting that the traditional categorization of different cortical areas into resting state and task related does not accommodate the functions of this parietal area. This part of the brain functions in a modulating manner, in the sense that the deactivations of the caudal IPC, relative to cognitive demand, contributes to task performance. The more difficult the task is or rather the higher the cognitive demand is, the more the number of negative functional connectivity of the caudal IPC with both task and resting state-related parts of the cortex would be observed.

6.4 Connectivity profile of middle IPC

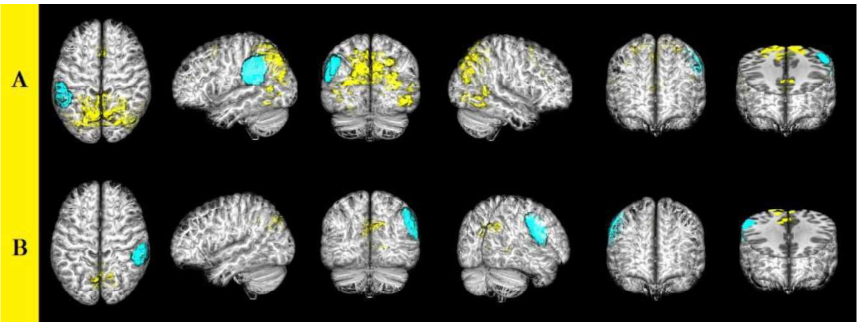
According to our findings, the connectivity patterns of the middle IPC are very similar to those of the caudal IPC (Tabassi Mofrad & Schiller, 2023), by having negative couplings with different parts of the visual cortex, the precuneus cortex, in addition to the anterior division of the cingulate gyrus, and the paracingulate gyrus, which are cognitive control-related parts of the brain (Jobson et al., 2021; Kragel et al., 2018).

In previous studies, the functions of the cingulate gyrus anterior division, in different executive functions such as decision making, task monitoring, error prediction (Khamassi et al., 2015; Shenhav et al., 2016;

Silvetti et al., 2013) and the involvement of the paracingulate gyrus in cognitive control (Kragel et al., 2018) have been elaborated on. The negative functional connectivity of the middle IPC with such brain areas underline that the middle IPC does not contribute to cognitive control either.

Figure 6.5

Demonstration of brain areas that the middle IPC is functionally connected with, in the more demanding context.

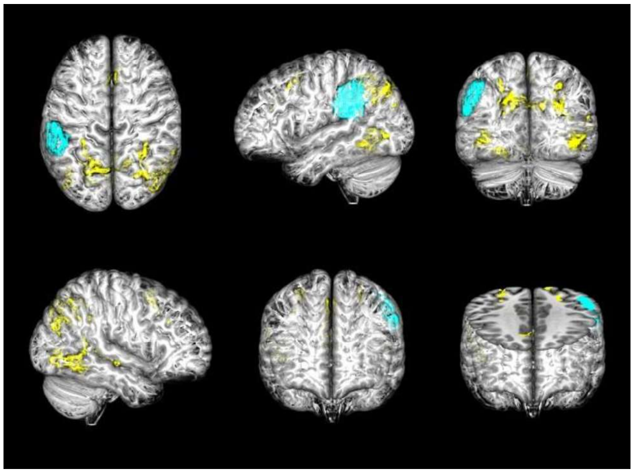


Note. The yellow color demonstrates brain areas that the middle IPC (shown in cyan) is functionally connected with, in the more demanding context of cognitive control. The descriptions of each row are as follows: A) negative functional connectivity of the left middle IPC with the precuneus cortex, the inferior division of the lateral occipital cortex, the anterior division of the cingulate gyrus, the occipital fusiform gyrus, and the lingual gyrus, B) negative functional connectivity of the right middle IPC with the precuneus cortex and the intracalcarine cortex.

The negative functional associations of the middle IPC is influenced by cognitive demand, with the more cognitively demanding condition, resulting in more negative functional couplings with other parts of the brain (see Figures 6.5 & 6.6). Besides, the negative functional associations of the middle IPC do not indicate that this part of the brain is resting state-related because of its negative coupling with the precuneus cortex – a brain area with reduced activity when performing a task. Furthermore, the middle IPC has negative connectivity with different parts of the visual cortex; improving cognitive performance, by better visualizing the stimuli, is the result of positive functional coupling of brain areas involved in cognitive control with the visual cortex. The absence of such positive functional associations of the middle IPC with e.g. the lateral occipital cortex, the occipital fusiform gyrus, and the lingual gyrus emphasize that this parietal area does not contribute to general cognitive functions and is not a task-related part of the cortex.

Figure 6.6

Demonstration of brain areas that the middle IPC is functionally connected with, in the less demanding context.



Note. The yellow color demonstrates brain areas (the inferior and posterior divisions of the lateral occipital cortex, the paracingulate gyrus and the anterior division of the cingulate gyrus) that the left middle IPC (shown in cyan) has negative functional connectivity with, in the less demanding context of cognitive control.

The connectivity profile of the middle IPC has highlighted the distinctive functions of this part of the cortex, characterized with deactivations in functionally coupling with other brain areas, in a modulating manner, proportional to the level of cognitive demand. In fact, the connectivity patterns of the middle IPC, similar to those of the caudal IPC, are not explained by the classic categorization of brain areas as resting-state and task-related, which advanced our hypothesis about modulating cortical areas.

6.5 Conclusion

The connectivity profiles of the clusters of the IPC elucidate that it is not the whole IPC that is involved in cognitive control but only the rostral cluster of this brain area (Tabassi Mofrad & Schiller, 2020) - with the middle and the caudal IPC demonstrating negative associations with parts of the brain that are engaged in executive functions (Tabassi Mofrad & Schiller, 2022; 2023). In previous studies, by ignoring the tripartite structure of the IPC, if the experimental conditions necessitated cognitive control, the functions of the rostral IPC were generalized to the whole IPC. However, if the experiment was conducted during the resting state or in the absence of an explicit task, the negative functional associations of the middle and the caudal IPC were considered representative of the whole IPC; hence, the contradictory research results on how this part of the brain functions.

Given the unique connectivity profiles of the middle and the caudal IPC, we considered modulating roles for these parietal areas, which demonstrate negative functional couplings with different parts of the visual cortex, cognitive control-related parts of the brain and with the precuneus cortex (Tabassi Mofrad & Schiller, 2022; 2023); the more difficult the task is, the more negative functional associations of these clusters of the IPC with other brain areas would be observed, while their connectivity profiles make them dissimilar to task-related and resting state-related parts of the cortex. In fact, the functional connectivity patterns of the middle and the caudal IPC evidence that the traditional categorization of brain areas does not accommodate the functions of such clusters of the IPC; the functional associations of the middle and the caudal IPC have highlighted another brain functional category beyond the classic definitions, as modulating cortical areas, the functional connectivity of which are disparate from parts of the cortex involved in task performance and brain areas related to the resting state functionality of the brain.

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Chapter 7

General discussion

7.1 Summary of the findings

This dissertation addressed whether individual differences in cognitive control of language are reflected by resting state networks involved in cognitive control, namely, the frontoparietal network (FPT), the default mode network (DMN), and the salience network (SN). By focusing on the inferior parietal cortex (IPC), and the connectivity profiles of the clusters of this part of the cortex, this dissertation elucidated that it is not the whole IPC that contributes to language control and it elaborated on modulating cortical areas.

7.1.1 Individual differences in cognitive control

As reported in Chapter 2, by doing the independent component analysis, ten independent components related to three intrinsic networks of interest involved in cognitive control of language, that is, the FPT, the DMN, and the SN, were detected in the participants of my study. Conducting dual regression on the identified independent components between groups of participants with better and poorer performance in cognitive control of language revealed that two subcomponents of the FPN, that is, the dorsolateral prefrontal cortex (DLPFC) and the inferior parietal cortex (IPC) were involved in individual differences in this executive function - in the sense that there was increased functional connectivity between the left primary somatosensory cortex and the DLPFC in participants with better performance in language control. However, in participants with poorer performance in the same cognitive control function, there was increased coupling between the right primary somatosensory cortex and the inferior parietal cortex.

The fact that the DLPFC and the IPC are involved in cognitive control, in particular, in tasks requiring switching between stimuli, has already been mentioned in previous studies (Collette et al., 2005; Derrfuss et al., 2005). However, what the present research added to the literature concerns the contribution of these two cortical areas to cognitive control, due to the functional connectivity of the primary somatosensory cortex with these brain areas, how such connectivity profiles characterize individual differences in cognitive control of language.

7.1.1.1 Primary somatosensory cortex and cognitive control

Generally, the left motor cortex is involved in mental rotation and motor control (Tomasino et al., 2005; Cona et al., 2017) if participants are right-handed. Since the somatosensory cortex converges to the motor cortex circuitry (for a review see Hooks, 2017), the functional connectivity between the DLPFC and the left primary somatosensory cortex in participants with better performance in cognitive control of language is indicative of using the left motor cortex circuitry to switch between languages. However, as the right primary somatosensory cortex apparently does not have the same efficient connections with the motor cortex circuitry, the functional connectivity between the IPC and the right primary somatosensory cortex marks poorer performance in switching between languages (see Chapter 2).

Reineberg et al. (2015) also reported the involvement of the primary somatosensory cortex in some executive functions such as working memory updating, task set shifting, and response inhibition, as reflected by the functional connectivity of this part of the cortex during resting state. They also emphasized the involvement of the somatosensory region in stimulus-response mapping when performing a task, as one of the reasons this part of the cortex is contributing to cognitive control. Since the DLPFC is also a cognitive control area, it seems that the functional coupling of the DLPFC and the left primary somatosensory creates a strong circuitry in cognitive control behavior. Besides, better performance in cognitive control of language - as indicated by the functional connectivity between the DLPFC and the left primary somatosensory in the present research (see Chapter 2) - has demonstrated that it is not the whole primary somatosensory cortex that contributes to cognitive control, but only the left part of this cortical area. This also highlights a dual function for the primary somatosensory cortex, depending on whether it is the left or the right side of this cortical area that couples with the sub-components of the FPN.

7.1.2 Contributions of rostral IPC to cognitive control

In Chapter 3, it is delineated how the rostral IPC contributes to cognitive control of language. As revealed by the psychophysiological interaction analyses, in language control, this part of the brain has asymmetrical and lateral functional connectivity with other cortical areas, modulated by cognitive demand.

7.1.2.1 Connectivity profile of rostral IPC in switching to L1

In the context of the language switching experiment, when switching to the L1, both the right and the left rostral IPC had negative functional connectivity with the precuneus cortex. Besides, there were negative functional coupling between the left rostral IPC and the superior frontal gyrus, and between the right IPC rostral cluster and the postcentral gyrus. However, there was positive coupling of the right IPC rostral cluster with the cerebellum (the posterior lobe, the declive). Switching to L1 is cognitively more demanding than switching to L2 (Meuter & Allport, 1999), and the way the precuneus cortex contributes to cognitive control is by reducing its activity and connectivity relative to the degree of the difficulty of the task. That is, the more difficult the task is, the more negative activity of the precuneus cortex would be observed (Dang, O'Neil & Jagust, 2013; Gilbert et al., 2012). Hence, the reason the rostral IPC demonstrated negative functional connectivity with this part of the cortex when switching to the L1.

The superior frontal gyrus as part of the prefrontal cortex, is involved in selecting a response among competing candidates and activating possible responses (Bunge et al., 2002). The present research corroborated the interconnection between this part of the cortex and the parietal area reported in previous studies. Regarding the postcentral gyrus, as the location of the primary somatosensory cortex, previous studies reported positive functional connectivity between this brain area and the fronto-parietal network in individuals with better performance in executive functions during resting state fMRI (Reineberg et al., 2015). Since in that study I used task-based fMRI, decreased functional connectivity between the rostral IPC and the superior frontal gyrus was observed when switching to the L1.

Though the involvement of the cerebellum in cognitive control is not fully understood, it is known that this subcortical area contributes to the higher order cognitive functions (Bellebaum & Daum, 2007), in addition to the language control network (Green & Abutalebi, 2013; Krienen & Buckner, 2009). That supports my finding of the interconnection between the rostral IPC and the cerebellum, in particular in the more cognitively demanding context.

7.1.2.2 Connectivity profile of rostral IPC in switching to L2

The psychophysiological interaction analyses also revealed that in switching to the L2, the right rostral IPC had positive functional connectivity with the anterior cingulate cortex (ACC) and the precentral gyrus. The ACC is involved in general speech monitoring (Christoffels, Formisano, & Schiller, 2007) and in monitoring conflict between languages and selecting the response language (Abutalebi et al., 2012). The ACC is also part of the language control network (Abutalebi & Green, 2008, 2016). Since the parietal areas also control response selection (Abutalebi et al., 2008), the positive coupling of the rostral IPC and the ACC, by forming a circuit for response selection, resulted in shorter reaction times in switching to the L2. On the other hand, the precentral gyrus affects the speed of responding (McGuire & Botvinick, 2010) and is involved in language switching (Hernandez et al., 2009; Luk et al., 2012). Previous studies also reported the interconnection between the fronto-parietal network and the precentral gyrus (Ma et al., 2014); the present research not only demonstrated the functional association of the rostral IPC and the precentral gyrus, but also specified that the precentral gyrus is involved in forward switching (switching to the L2) but not in backward switching. Moreover, the connectivity of the rostral IPC and the precentral gyrus highlights the facilitatory function in faster L2 production in the language switching context.

7.1.2.3 Connectivity profile of rostral IPC modulated by cognitive demand

As explained in Chapter 3, cognitive demand modulated the connectivity patterns of the rostral IPC with other parts of the cortex. That resulted in differences in the type of functional connectivity and in laterality, when switching to the L1 (associated with higher cognitive demand) and switching to the L2 (associated with lower cognitive demand). While in switching to the L1, both negative and positive functional connectivity of the rostral IPC with other brain areas was observed, switching to the L2 was only associated with positive functional coupling of this part of the cortex. Furthermore, while both the right and the left rostral IPC had connectivity with other brain areas in switching to the L1, it is only the right rostral IPC that had functional associations when switching to the L2. Thus, the more cognitively demanding context of my experiments resulted in recruiting more underlying neural resources in a bilateral manner.

7.1.3 Unique connectivity profile of caudal IPC

As elaborated in Chapter 4, the functional connectivity analyses of the caudal IPC demonstrated that this part of the cortex had no similarity to a cognitive control area. More importantly, the caudal IPC showed negative functional connectivity with both the precuneus cortex, which is resting state-related, and other brain areas involved in processing general cognitive functions, in addition to cognitive control-related parts of the cortex. The connectivity profile of the caudal IPC provided enough evidence for the idea that the traditional categorization of different cortical areas into resting state and task related could not accommodate the functions of this part of the brain. Hence, the hypothesis for a new brain functional category as a modulating cortical area.

7.1.3.1 Lateral connectivity patterns of caudal IPC

Both in switching to the L1 and to the L2, the caudal IPC demonstrated heavily left lateralized functional connectivity with other parts of the brain. However, the way the rostral and the caudal IPC showed lateral coupling is different from each other. Firstly, the laterality in functional associations of the rostral IPC - with this cortical area being involved in cognitive control - is determined by the cognitive demand, but the caudal IPC is not involved in cognitive control. In addition, the lateral functioning of this cortical area does not appear to be language related. The reason is that the left lateralized functional connectivity of the caudal IPC comes from the negative coupling of this brain area with other parts of the cortex, e.g., parts of the brain involved in general cognitive functions such as visual cortex, cognitive control related brain areas, and even part of the brain related to resting state, i.e., the precuneus cortex. However, the left lateralized function of the brain that previous studies reported in processing language is the result of positive activations and functional connectivity of language related left cortical areas. Besides, the general connectivity patterns of the caudal IPC make this part of the cortex different from resting state and task related parts of the brain.

7.1.3.2 Similar connectivity profiles of caudal IPC in switching to L1 and L2

The left caudal IPC demonstrated negative coupling with the frontal pole, the anterior part of the prefrontal cortex, in both L1 and L2 switching contexts. This cortical area contributes to cognitive control and in general it is involved in higher-order cognitive functions (Hartogsveld et al., 2018; Zanto & Gazzaley, 2013). However, the negative functional connectivity of the caudal IPC with the frontal pole shows that the caudal IPC does not function like a cognitive control area.

The caudal IPC also demonstrated negative functional connectivity with the lateral occipital cortex, the inferior division, in switching to L1 and to L2. While positive coupling between the FPN and the visual cortex would result in better cognitive abilities such as word recognition (Twait & Horowitz-Kraus, 2019) and reading (Horowitz-Kraus & Holland, 2015), the lack of a positive fluctuation between the caudal IPC and the lateral occipital cortex shows that this parietal area is not involved in other cognitive functions.

7.1.3.3 Different connectivity profiles of caudal IPC in switching to L1 and L2 switching

In comparison, in switching to the L1, which is cognitively more demanding than switching to the L2, the caudal IPC demonstrated more negative functional connectivity with other brain areas in different parts of the visual cortex, resting state-related cortical areas, and other part of the cortex related to cognitive control. Those brain areas include the fusiform gyrys, posterior division, the cuneal cortex and the lingual gyrus in the visual cortex, the precuneus cortex, and the cingulate gyrus, anterior division. When switching to L2, the caudal IPC did not have functional connectivity with such brain areas. Instead, the caudal IPC had negative functional connectivity with other parts of the visual cortex, that is, the lateral occipital cortex, superior division, which was not observed when switching to the L1. Having said that, the posterior fusiform gyrus, the cuneal cortex, the lingual gyrus (relating to switching to the L1), and the lateral occipital cortex, superior division (relating to switching to the L2) are all part of the visual cortex. The negative functional association of the caudal IPC with the visual cortex, as mentioned before, evidences that this cortical area is not involved in general cognitive functions. Besides, the negative functional connectivity of the caudal IPC with the precuneus cortex was observed when switching to the L1 which is cognitively more demanding. Regarding cognitive control areas, while in both L1 and L2 switching conditions, the caudal IPC had negative functional connectivity with the frontal pole, in switching to the L1, the seed region also had negative connectivity with the anterior cingulate gyrus. The negative coupling of the caudal IPC with more cognitive control areas when the task is cognitively more demanding also points to the modulating function of the caudal IPC.

7.1.3.4 Modulating function of caudal IPC

Since in performing the language switching experiment, the caudal IPC showed negative coupling with the precuneus cortex, this parietal area cannot be associated with the resting state brain areas. Likewise, the negative coupling of the caudal IPC with cognitive control areas evidences that this part of the brain does not contribute to cognitive control in the FPN. Furthermore, the negative connectivity of the caudal IPC with different parts of the visual cortex shows that this brain area is not involved in general cognitive functions. Thus, the caudal IPC is not a task-related part of the brain.

The present research revealed that the traditional categorization of brain areas does not explain the connectivity profile of the caudal IPC. This cortical area functions in a modulating manner, in the sense that the deactivations of the caudal IPC, relative to task difficulty, contributes to task performance. The more difficult the task is or rather the higher the cognitive demand is, the more the number of negative functional connectivity of the caudal IPC with both task and resting state-related parts of the brain would be observed. Hence, the modulating role of this part of the cortex.

7.1.4 Connectivity profile of middle IPC

In Chapter 5, the connectivity profile of the middle IPC in the context of the language switching experiment was investigated, by which the hypothesis about the modulating cortical areas was advanced.

The connectivity patterns of the middle IPC, similar to those of the caudal IPC, were highly lateralized - independent of the cognitive demand - while being negatively connected with different parts of the visual cortex, the precuneus cortex and the anterior division of the cingulate gyrus, in addition to the paracingulate gyrus which is also involved in cognitive control functions (Jobson et al., 2021; Kragel et al., 2018). At the same time, the negative functional associations of the middle IPC was influenced by cognitive demand, with the more cognitively demanding experimental condition, resulting in more negative functional connectivity with other parts of the brain.

The connectivity profile of the middle IPC demonstrates that this part of the cortex, like the caudal IPC, is not a cognitive control area due to its negative functional connectivity with the anterior division of the cingulate gyrus and the paracingulate gyrus. Moreover, the negative functional associations of the middle IPC do not mean that this part of the brain is resting state-related because of its negative coupling with the precuneus cortex. Moreover, the negative connectivity of this parietal area with different parts of the visual cortex suggests that the middle IPC does not contribute to general cognitive functions and is not a task-related part of the cortex.

Similar to the caudal IPC, the connectivity profile of the middle IPC is not explained by the classic categorization of brain areas as resting state and task-related, further supporting the hypothesis about modulating cortical areas.

7.2 Integration of findings

According to the structural properties of the IPC, this part of the brain consists of three clusters, namely, the rostral, the middle and the caudal (Caspers et al., 2006; 2013). Based on the idea that the functional characteristics of the sub-regions of the IPC are underlined by their structural organization and given the inconsistent nature of research findings on how the IPC functions, under the same experimental conditions I investigated the functional connectivity profiles of the clusters of the IPC in a task which required cognitive control of language, with two different levels of cognitive demand.

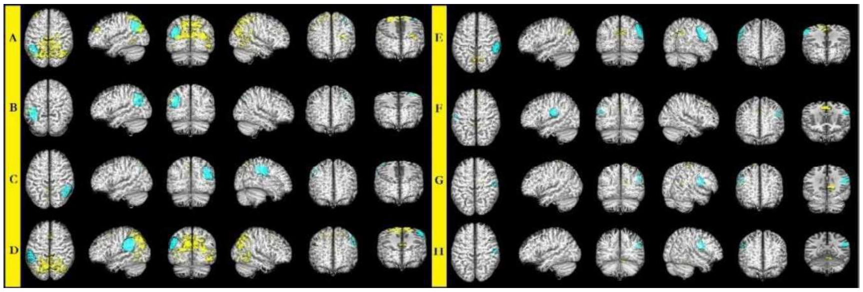
Research findings (Figures 7.1 & 7.2) revealed that it is not the whole IPC that is involved in cognitive control but only the rostral cluster of this brain area (Tabassi Mofrad & Schiller, 2020). The rostral IPC via positive functional connectivity with the anterior division of the cingulate gyrus, the precentral gyrus and the posterior lobe of the cerebellum, forms a strong response selection circuit in the frontoparietal network, facilitates cognitive control of language and further evidences its involvement in the language control network, respectively.

The caudal IPC, however, is not only characterized with entirely different connectivity patterns as those of the rostral IPC but proves lack of involvement in cognitive control (Tabassi Mofrad & Schiller, 2022). Firstly, this brain area has negative functional connectivity with different parts of the visual cortex. Given this is the positive functional association between brain areas involved in cognitive control and the visual cortex that improves cognitive performance, the negative coupling of the caudal IPC with e.g., the inferior and posterior divisions of the lateral occipital cortex, the cuneal cortex, the temporal occipital fusiform, and the lingual gyrus highlight the type of functional connectivity which is dissimilar to those of cognitive control-related parts of the cortex. In addition, the caudal IPC has negative functional associations with the frontal pole as well as the anterior division of the cingulate gyrus. While these brain areas are heavily involved in processing executive functions, such negative functional associations show that the caudal IPC is not involved in processing cognitive control in the frontoparietal network. Furthermore, it is revealed that this cluster of the IPC also has negative functional connectivity with the precuneus cortex which is a resting state-related part of the brain.

Taking into account that brain areas that are involved in task performance decrease activity during the resting-state, and those parts of the cortex that are active in the absence of external stimuli decrease activity when involved in a task, the negative functional connectivity of the caudal IPC with the precuneus cortex indicates that the caudal IPC is not resting state-related part of the brain. Having negative connectivity patterns with both the resting-state and the task based-related cortical areas characterize the caudal IPC with a distinctive function, highlighting that the traditional classification of brain areas as being active either when involved in a task or when not focusing on external stimuli cannot explain the behavior of the caudal IPC.

Figure 7.1

Demonstration of the clusters of the IPC and brain areas that the seed regions had functional connectivity with, when switching to L1.

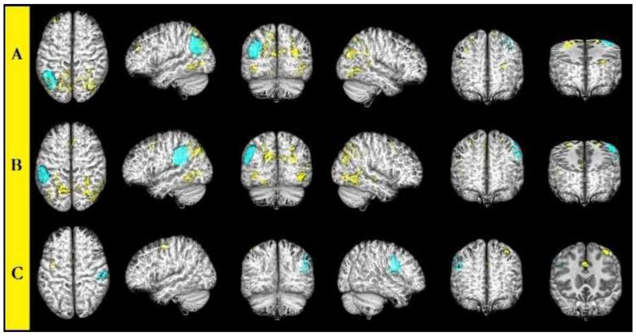


Note. The yellow color demonstrates brain areas that the clusters of the IPC (shown in cyan) are functionally connected with, under the more demanding context of cognitive control of language. The descriptions of each row are as follows: A) negative functional connectivity of the left caudal IPC with the precuneus cortex, the inferior and posterior divisions of the lateral occipital cortex, the frontal pole, the anterior division of the cingulate gyrus, the posterior division of the temporal occipital fusiform and the lingual gyrus, B) positive functional connectivity of the left caudal IPC with the IPC caudal cluster left (PGa), C) negative functional connectivity of the right IPC with the cuneal cortex, D) negative functional connectivity of the left middle IPC with the precuneus cortex, the inferior division of the lateral occipital cortex, the anterior division of the cingulate gyrus, the occipital fusiform gyrus, and the lingual gyrus, E) negative functional connectivity of the right middle IPC with the precuneus cortex and the intracalcarine cortex, F) negative functional connectivity of the left rostral IPC with the superior frontal gyrus and the precuneus cortex, G) negative functional connectivity of the right rostral IPC with the postcentral gyrus and the precuneus cortex, H) positive functional connectivity of the right rostral IPC with the posterior lobe of the cerebellum.

The negative functional connectivity of the caudal IPC with other parts of the brain is influenced by cognitive demand - the more demanding the task is, the more negative functional connectivity of this subdivision of the IPC with both the resting state-related and the cognitive control-related brain areas would be observed. Therefore, it is the decreased activation in the functional connectivity of the caudal IPC with other parts of the brain, relative to the level of cognitive demand, that contributes to task performance.

Figure 7.2

Demonstration of the clusters of the IPC and brain areas that the seed regions had functional connectivity with, when switching to L2.



Note. The yellow color demonstrates brain areas that the clusters of the IPC (shown in cyan) are functionally connected with, under the less demanding context of cognitive control of language. The descriptions of each row are as follows: A) negative functional connectivity of the left caudal IPC with the inferior and posterior divisions of the lateral occipital cortex and the frontal pole, B) negative functional connectivity of the left middle IPC with the inferior and posterior divisions of the lateral occipital cortex, the paracingulate gyrus and the anterior division of the cingulate gyrus, C) positive functional connectivity of the right rostral IPC with the precentral gyrus and the anterior division of the cingulate gyrus.

Given such unique connectivity profile of the caudal IPC, I considered a modulating role for this brain area. My assumption on such a concept was further confirmed having observed the functional connectivity patterns of the middle IPC which are comparable to those of the caudal IPC, by demonstrating negative functional connectivity with similar parts of the visual cortex, with cognitive control-related parts of the brain and with the precuneus cortex, which is resting state-related (Tabassi Mofrad & Schiller, 2023). The middle inferior parietal cortex is likewise characterized with more negative functional associations with other parts of the brain when the task is more demanding, while its connectivity profile makes this cortical area dissimilar to task-related and resting state-related parts of the cortex.

The connectivity profiles of the clusters of the IPC that I have discussed elucidate that only the rostral IPC is involved in processing cognitive control - with the middle and the caudal IPC demonstrating negative connectivity with parts of the brain that are engaged in executive functions, such as the frontal pole, the paracingulate gyrus and the cingulate gyrus anterior division. Moreover, the functional connectivity patterns of the middle and the caudal IPC have highlighted another brain functional category beyond the classic definitions, as modulating cortical areas, the functional associations of which are disparate from parts of the cortex that are involved in task performance and brain areas which are active during the resting-state.

7.3 Limitations and future research

For the studies reported in this dissertation, participants' behavioral data from a language switching experiment were collected four weeks after their neuroimaging data were acquired in the MRI lab. This procedure is in line with previous studies (e.g., Anderson et al., 2018; Grady et al., 2015). However, it is also possible to collect the behavioral data at the same time when participants do the experiment inside the MRI scanner by using an MRI compatible microphone. Using such a microphone - although being very expensive - obviates the need for the researcher to repeat the experiment, and that would save time both for the researcher and for the participants. Unfortunately, however, I did not have access to such a microphone at the time.

In this dissertation, I presented the research results from resting-state fMRI and task-based fMRI, by which it became clear that it is only the rostral part of this cortical area that contributes to cognitive control in the FPN - among other findings. In contrast, the middle and the caudal IPC have distinctively modulating functions marked by their deactivation in task performance relative to the degree of the cognitive demand of the task while such functions are not similar to parts of the cortex involved in resting-state. Future research may investigate the white matter connectivity of the rostral, the middle, and the caudal IPC to examine whether different functional profiles of the clusters of the IPC are also reflected by white connectivity with other parts of the brain.

In this study, I recruited healthy individuals without any report and history of neurological or psychiatric problems. Future research may address the functional connectivity profiles of the clusters of the IPC in individuals with dysfunction in cognitive control to examine how the cognitive control functions of the rostral IPC and the modulating roles of the middle and the caudal IPC would demonstrate different patterns of activity, to contribute to the literature of clinical neuroscience.

7.4 Conclusion

Resting state functional connectivity of brain areas in the FPN reflected individuals' performance related to cognitive control. The present research demonstrated that the connectivity of DLPFC with the left primary somatosensory cortex (BA1) and the association of the inferior parietal cortex with the right primary somatosensory cortex (BA2) indicate better and poorer performance in cognitive control of language, respectively. Moreover, during task-based fMRI the connectivity profile of the rostral IPC was not only modulated by the cognitive demand both asymmetrically and laterally, but this part of the brain also proved to contribute to cognitive control in the FPN - while that is not the case with the middle and the caudal IPC. The functional connectivity of these two cortical areas revealed that they have negative functional associations in a modulating manner not only with some cortical areas in the FPN – suggesting that they are not part of the control network – but also with brain areas involved in general cognitive functions such as the visual cortex. At the same time the connectivity profile of the middle and the caudal IPC have no similarity to those of the resting state-related cortical areas. In fact, in task performance, the middle and the caudal IPC demonstrated deactivations in the patterns of their functional connectivity, influenced by cognitive demand. In the more demanding context, the number of the negative functional couplings of these parts of the cortex with other brain areas increased. However, that does not associate the middle and the caudal IPC with the resting-state parts of the brain as these parietal areas also demonstrated negative connectivity with the precuneus cortex. The present research revealed that the traditional categorization of cortical areas as task-related and resting state-related cannot accommodate the functions of the middle and the caudal IPC, by which I hypothesized a functional brain category, beyond classic definitions, namely modulating cortical areas.

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Samenvatting in het Nederlands

De inferieure pariëtale cortex (IPC) is een complex hersengebied met de rostrale, de middelste en de caudale clusters, en functioneel verbonden met verschillende andere corticale gebieden. Er wordt gesuggereerd dat verschillende cognitieve functies worden bestuurd door de IPC, maar omdat de tripartiete structuur van dit deel van de hersenen wordt genegeerd, zijn er in de literatuur veel tegenstrijdige onderzoeksrapporten.

In mijn onderzoek heb ik onderzocht hoe de clusters van de IPC bijdragen aan cognitieve controle van taal met behulp van multiband EPI. Volgens de bevindingen, wanneer de context wordt gekenmerkt door minder cognitieve vraag, had de rechter rostrale IPC een positieve functionele connectiviteit met het voorste deel van de cingulate gyrus en de precentrale gyrus. In de meer cognitief veeleisende context had de rechter IPC rostrale cluster echter een negatieve functionele koppeling met de postcentrale gyrus en precuneus cortex en positieve connectiviteit met de achterste kwab van het cerebellum. In deze toestand had de linker IPC-rostrale cluster een negatieve functionele koppeling met de superieure frontale gyrus en de precuneuscortex. Aldus werden de connectiviteitspatronen van de rostrale IPC beïnvloed door cognitieve vraag op een asymmetrische en laterale manier tijdens cognitieve controle van taal.

Onder dezelfde experimentele omstandigheden vertoonde de caudale IPC functionele connectiviteitspatronen die niet vergelijkbaar waren met een cognitief controlegebied en tegelijkertijd vertoonde dit pariëtale gebied negatieve functionele associaties met zowel taakgerelateerde hersengebieden als de precuneuscortex, die is actief tijdens de rusttoestand. Ik vond bewijs dat de traditionele indeling van verschillende hersengebieden in taakgebaseerde en rustgerelateerde netwerken niet de functies van de caudale IPC aanpakt. Dit ondersteunt de hypothese over een nieuwe hersenfunctiecategorie als modulerend corticaal gebied, wat suggereert dat zijn betrokkenheid bij taakuitvoering, op een modulerende manier, wordt gekenmerkt door deactivering in de patronen van zijn functionele associaties met delen van de hersenen die betrokken zijn bij taakuitvoering, in verhouding tot de moeilijkheidsgraad van de taak; de patronen van zijn functionele connectiviteit komen echter in sommige andere opzichten niet overeen met de rusttoestand-gerelateerde delen van de cortex. De middelste IPC vertoonde ook vergelijkbare connectiviteitspatronen als die van de caudale IPC, wat mijn hypothese over het moduleren van corticale gebieden bevestigde.

De connectiviteitsprofielen van de clusters van de IPC maken duidelijk dat niet de gehele IPC betrokken is bij cognitieve controle, maar alleen de rostrale cluster van dit hersengebied - waarbij de middelste en caudale IPC negatieve associaties vertonen met delen van de hersenen die betrokken zijn bij uitvoerende functies. In eerdere studies werden, als gevolg van het negeren van de tripartiete structuur van de IPC, de functies van de rostrale IPC gegeneraliseerd naar de hele IPC wanneer de experimentele omstandigheden cognitieve controle noodzakelijk maakten; als het experiment echter werd uitgevoerd tijdens de rusttoestand of bij afwezigheid van een expliciete taak, werden de negatieve functionele associaties van de middelste en de caudale IPC als representatief beschouwd voor de hele IPC; vandaar de tegenstrijdige onderzoeksresultaten over hoe dit deel van de hersenen functioneert. De unieke connectiviteitsprofielen van de middelste en caudale IPC hebben echter een andere hersenfunctionele categorie onderstreept, buiten de klassieke definities, namelijk modulerende corticale regio's, waarmee de tegenstrijdige onderzoeksresultaten in eerdere studies worden aangepakt.

In mijn onderzoek heb ik ook onderzocht of individuele verschillen in cognitieve controle van taal worden weerspiegeld door de intrinsieke functionele connectiviteit van de hersenen. Volgens de bevindingen is er een verhoogde koppeling van de linker primaire somatosensorische cortex met de dorsolaterale prefrontale cortex bij proefpersonen met een betere cognitieve controle van taal en een verhoogde koppeling van de rechter primaire somatosensorische cortex met de inferieure pariëtale cortex in de groep met slechtere prestaties in deze uitvoerende functie. Met betrekking tot deze resultaten stelde ik voor dat de primaire somatosensorische cortex een dubbele functie heeft bij het verbinden met de dorsolaterale prefrontale cortex en de inferieure pariëtale cortex in het frontoparietale netwerk, en dat kenmerkt tweetalige individuele verschillen in cognitieve controle van taal. Dergelijke resultaten kunnen dienen als referentie in de klinische neurowetenschappen wanneer tweetaligen worden gediagnosticeerd met disfunctie in cognitieve controle.

Curriculum vitae

Fatemeh (Simeen) Tabassi Mofrad was born in Tehran, in 1979. She completed her Bachelor's degree in English Language and Literature at Alzahra University, in Tehran, in 2011, and graduated with distinction. She then completed a Master's degree in Applied Linguistics at Tarbiat Modares University, in Tehran, in 2013, which was followed by completion of a PhD degree in Applied Linguistics, also at Tarbiat Modares University, in 2019; for both postgraduate programs, she was exempt from Iran's nationwide university entrance exam, issued by Iran's Exceptional Talents Organization. Simeen completed over 40 extra modules in Psychology, Linguistics, Education, and Neuroscience, at Tarbiat Modares University, University of Southern Denmark, and University College London, and she was awarded Qualification for Academic Teaching by Tarbiat Modares University. During her postgraduate studies in Iran, Simeen was offered lectureship and for five years she worked as a lecturer in Tehran, before she started her second PhD in Cognitive Neuroscience at Leiden University. Alongside her second PhD, Simeen also started research/teaching collaborations with University of Warwick, City University London and University College London, with being the (Master's) module leader in Cognition and Neuropsychology at University of West London. Simeen has multiple successful experieces in securing travel/research funds, e.g. during her PhD program in Leiden, she was awarded €25,000 by Leiden University Fund/Gratama Foundation for her project in Genetics of Cognitive Neuroscience and she was subsequently inducted into Leiden University Hall of Fame. Besides, Simeen's most recent research discoveries (Chapter 4 of this dissertation) received press coverage e.g. by Neuroscience News, Medical Express, and Australia's Mirage News, among others. Simeen has multidisciplinary research perspectives and she develops projects in many different diverse fields of research; fMRI and DTI are her favorite neuroimaging techniques.