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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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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 Canada (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, suppressing 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; Keyzers & 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 test¹ 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.

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 software²(*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 SRBOX³ (Serial Response BOX) was used to collect their RTs.

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 psychological 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 MELODIC⁴ (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

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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