Mapping the Spatiotemporal Interactions of the Human Brain’s Attention Reorienting and Arousal Systems Using Multimodal Recording Techniques

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The human brain is remarkably good at identifying stimuli worthy of attention, and efficiently allocating its limited neural resources. In the context of an attention reorienting task, where subjects are required to process novel and unexpected incoming sensory information and transform them into actions, the goal for the brain is therefore to orient attention to the most task-relevant stimulus so as to facilitate stimulus processing and behavioral outcome. Recent studies suggest that arousal plays a role in modulating attention reorienting, task engagement, and performance optimization. The rising interest and studies notwithstanding, the exact mechanism and function of arousal in attention reorienting still remains largely elusive.

The aim of this dissertation is to investigate the interactions between arousal and attention reorienting systems, and the spatiotemporal dynamics of such interactions. Specifically, we simultaneously record pupillometry, electroencephalography (EEG), and functional magnetic resonance imaging (fMRI) to study the fluctuations of the latent states, while subjects perform an auditory oddball task. The oddball task is used to drive the attention reorienting response, and to control for potential ocular confounds that might be induced with a visual paradigm. With concurrently recorded cross modality data, we explore different aspects of the potential interactions between arousal and attention reorienting systems using various combinations of modality-specific trial-to-trial variabilities. We find baseline pupil-linked arousal is correlated to EEG variability temporally localized at a time after the behavioral response, and spatially linked to intrinsically-driven and executive-function related regions; whereas stimulus-driven pupil-linked arousal is temporally related to EEG variability closer to the stimulus onset, and spatially correlated to task-relevant regions. Taken together, our work in this dissertation uses innovative data acquisition and analysis
approaches to provide a novel spatiotemporal mapping of the interactions between arousal and attention reorienting systems. Our findings offer new insight on the mechanism and function of how human orients attention, and how arousal is linked to such seemingly trivial yet fundamentally significant cognitive function.
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Table 9.1  **BOLD correlates of oddball pupil diameter baseline STV regressor in pupil-STV modulated fMRI analysis.** Significant clusters resulting from pupil diameter baseline STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, MaxZ column presents the maximum z-score of the cluster, $P^{\text{clus}}_{FWE}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.

Table 9.2  **BOLD correlates of oddball PR STV regressor in pupil-STV modulated fMRI analysis.** Significant clusters resulting from PR STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, MaxZ column presents the maximum z-score of the cluster, $P^{\text{clus}}_{FWE}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.

Table 10.1  **BOLD correlates of oddball PDB x EEG STV regressor in oddball pupil diameter baseline x EEG-STV modulated fMRI analysis.** Significant clusters resulting from PDB x 525ms Oddball EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, MaxZ column presents the maximum z-score of the cluster, $P^{\text{clus}}_{FWE}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
Acknowledgments

One afternoon a week before my thesis defense, I was sitting in the conference room with Dr. Paul Sajda, my PhD advisor. We had just combed through some final changes with respect to my thesis and defense presentation, before Paul lowered his voice and asked, “Can you imagine you are going to be done in a week?”

I absolutely could not. At a point where I had fully accepted only change is constant, the definitive fact that I would finally be concluding my PhD seemed rather unimaginable, if not slightly surreal.

Nevertheless, the finish line is indeed in sight, and the first person I wish to thank for making this journey possible, is Paul. I am extremely grateful for his support and guidance, but above all, for the freedom, the trust, and the never failing availability he had so amazingly offered.

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“The mind of man is capable of anything — because everything is in it, all the past as well as all the future. What was there after all?”

Joseph Conrad, in *Heart of Darkness* [Conrad, 1902].
Chapter 1

Overview

1.1 Motivation

“To be or not to be”, that is not just Shakespeare’s question. The world is filled with scenarios which call for our attention, be it as simple as when to cross the street, or as complicated as in Hamlet. These scenarios come in various forms, which dictate the different ways in which we direct our attention. For goals or expectations to be fulfilled, we would voluntarily shift our attention to them; whereas for sudden or particularly salient stimuli, our attention would be drawn involuntarily. Often times, even with identical sensory input, our reaction or behavior may still vary.

How does the human brain carry out these seemingly elementary yet fundamentally significant functions? Why would one’s reaction be different even when the stimulus remained the same? These questions prompted us to study attention and its reorienting mechanism, together with the hidden yet potentially crucial factor, arousal.

1.2 The attention reorienting and arousal systems

[Posner and Petersen, 1990] first proposed the idea that the human attention system is composed of three networks: 1) an alerting network, 2) an orienting network, and 3) an executive network [Posner and Petersen, 1990, Petersen and Posner, 2012]. Their publication formed the basis for numerous attention based studies, with some major advances in the recent years implicating additional or alternative networks in attention modulation. In more specific terms, the alerting network focused
mainly on the arousal systems, with the orienting network focusing on the human brain’s ability
to prioritize sensory input by selecting a modality or location, and the executive network focusing

The interplay between these various networks notwithstanding, the focus of this dissertation
lies in the putative arousal, and the orienting systems. Specifically, the goal of this dissertation
is to examine the dynamics, and especially the dynamics of the interactions between the arousal
and the attention reorienting systems. In this opening chapter, we will introduce these two major
systems, along with physiological or neural indicators that could be exploited to index the activity
of core regions involved in each system.

1.2.1 The reorienting system

First, what is the purpose of reorienting attention? To safely navigate the environment, survive,
and reproduce, animals and humans must rapidly select sensory information that is relevant to their
goals (e.g., routes, food, mates). They must also quickly redirect their attention and change their
course of action when faced with novel, potentially threatening, or rewarding stimuli [Corbetta
et al., 2008]. As it is simply impossible for the brain to process all the events that happen in
the environment, it is important to identify the stimulus which is worthy of our attention. After
this initial selection, it is equally important to allocate the brain’s limited processing power in an

The complex set of adjustments in response to novel and unexpected stimuli is defined here as a
reorienting response. Reorienting may occur between two environmental stimuli, such as when we
orient to the siren of an ambulance while reading a newspaper, or between an internally directed
activity and the environment, as when the same siren interrupts a train of thought [Corbetta et al.,
2008].

A classical context to study the mechanism of attention reorienting, is in a target detection task.
This type of task requires the brain to process novel and unexpected incoming sensory information
and transform them into actions. The goal for the brain in such tasks is twofold: to orient attention
to the most task-relevant stimulus so as to facilitate stimulus processing, and to optimize behavior
so as to benefit the outcome. Previous work indicates that this adaptive behavior involves a complex
interaction between cortical systems specialized for the selection of sensory information, with more
recent work suggesting arousal, as another potential contributor to the brain’s activations related to unexpected stimuli [Aston-Jones and Cohen, 2005, Yu and Dayan, 2005, Corbetta et al., 2008].

[Corbetta et al., 2008] reviewed in great detail the two cortico-cortical neural systems that are involved in attending to environmental stimuli, especially in the scenario of attention reorienting. The two putative systems are the dorsal frontoparietal network, and the ventral frontoparietal network. The brain’s reorienting response involves the coordinated action of a right hemisphere dominant ventral frontoparietal network that interrupts and resets ongoing activity and a dorsal frontoparietal network specialized for selecting and linking stimuli and responses. At rest, each network is distinct and internally correlated, but when attention is focused, the ventral network is suppressed to prevent reorienting to distracting events [Corbetta et al., 2000, Corbetta and Shulman, 2002, Corbetta et al., 2008].

1.2.2 The arousal system

In addition to the reorienting system, several neuromodulatory systems have also been linked to the detection of unexpected events, including the locus coeruleus/norepinephrine (LC-NE) system [Aston-Jones and Cohen, 2005, Yu and Dayan, 2005, Bouret and Sara, 2005, Dayan and Yu, 2006, Corbetta et al., 2008]. The LC is a small nucleus in the brainstem that plays a central role in the regulation of arousal through the release of NE (see top panel of Figure 1.1) [Berridge and Waterhouse, 2003, Sara, 2009, Eckstein et al., 2017]. In the context of this thesis, arousal refers to a physiological and cognitive state, and needs to be carefully distinguished from attention. The broadest categorization of arousal is whether an individual is awake or asleep, although it may be more accurate to view neural arousal as falling along a continuum whose extremes are deep sleep and being fully awake. Individuals who are awake, therefore, can operate at different levels of arousal or alertness. An alert person typically is fully awake, and attends intently to the local environment. In contrast, people who are drowsy are less attentive to the events going on around them [Purves et al., 2012]. Attention, on the other hand, has the key nature of being selective. Attention can be, and typically is, selectively focused. As described above, selective attention refers to the allocation of processing resources to the analysis of certain stimuli or aspects of the environment, generally at the expense of resources allocated to other concurrent stimuli or aspects [Bundesen, 1990, Wolfe, 1994, Purves et al., 2012].
It is generally accepted that there is not a single, unitary construct of arousal but, rather, a constellation of brain and somatic systems that subserve distinct but often overlapping functions - the LC-NE system is one of these systems [Pribram and McGuinness, 1975, Neiss, 1988, Robbins, 1997, Gilzenrat et al., 2010]. In fact, the role of the LC-NE system in arousal and its specific role in signal processing and cognition are intrinsically linked [Corbetta et al., 2008]. The LC neurons exhibit two modes of activity: the tonic and phasic mode. Both extremely low and high levels of tonic LC activity are accompanied by a lack of task-dependent phasic LC responses as well as poor task performance, whereas intermediate levels are accompanied by phasic responses to task-relevant stimuli and good task performance [Aston-Jones and Bloom, 1981, Abercrombie et al., 1988, Rajkowski et al., 1994, Aston-Jones et al., 1997, Usher et al., 1999, Aston-Jones and Cohen, 2005]. On a behavioral level, this inverted-U relationship has been famously described by [Yerkes and Dodson, 1908]. In more specific terms as demonstrated in the bottom panel of Figure 1.1, the left side of the inverted-U shaped curve corresponds to low tonic and absence of phasic LC activity, where subjects are drowsy and inattentive. The right side of the concave curve corresponds to high tonic and absence of phasic LC activity, where subjects are overly alert and easily distracted. Lastly, the middle part of the curve corresponds to intermediate tonic and the presence of phasic LC activity, and the subjects are most task engaged under such arousal level, and most likely to produce optimal performance.

Inspired predominately by studies of single-cell LC activity in animals (e.g., [Aston-Jones et al., 1994, Rajkowski et al., 1994]), a number of sophisticated theoretical models have been devised that implicates the LC-NE system in arousal [Murphy et al., 2014]. Traditionally, LC has been largely linked to the physiological states mediated by arousal. In the recent years, however, it has been hypothesized that the LC-NE system is responsible for various cognitive states related with arousal. Specifically, the system has been implicated in a broad array of core cognitive processes such as the regulation of task engagement [Usher et al., 1999, Aston-Jones and Cohen, 2005, Bouret and Sara, 2005, Sara and Bouret, 2012] and learning ([Yu and Dayan, 2005, Dayan and Yu, 2006, Murphy et al., 2014]).
Figure 1.1: The LC-NE system and its relationship to cognitive performance. (Top) The LC is the major source of cortical NE and has widespread and highly specific connections throughout the entire nervous system. The LC-NE system promotes arousal and is crucial for a variety of physiological as well as cognitive functions, such as attention, memory, and decision making. (Bottom) Task performance is optimal at intermediate levels of NE, at which task-relevant stimuli elicit pronounced phasic LC responses. Low levels of NE are associated with inattentive behavior and drowsiness, and high levels with distractibility. Adapted with permission from Eckstein et al., 2017, [Eckstein et al., 2017], used under CC BY-NC-ND 4.0 / Cropped from original. Copyright © 2016 The Authors. Published by Elsevier Ltd.
1.2.3 Interactions between the two systems

Taken together, the striking resemblance between the emergence of such neurocomputational theories of the LC-NE system activity and the proposed roles of the ventral attention network, seem to suggest a potential functional link between signals of the LC-NE system and activity in the ventral attention network [Shulman et al., 2003, Todd et al., 2005, Corbetta et al., 2008]. In other words, the different patterns of recruitment exhibited by the dorsal and ventral attention networks may reflect inputs to the ventral attention network from the LC-NE system [Shulman et al., 2003, Todd et al., 2005, Corbetta et al., 2008]. The rising interest and studies notwithstanding, the exact mechanism and function of arousal in attention reorienting still remains largely elusive. The aim for this thesis is to investigate the relationship and potential interactions between the arousal and attention reorienting systems, as well as their effects on stimulus processing and decision making in the context of a target detection task. Specifically, we wish to provide more insight on how different levels of arousal could affect both the control of attention, and the effect of attention on stimulus processing and decision making.

1.3 Three recording modalities

In order to study how arousal and attention reorienting are manifested through neural processes in a laboratory setting, an ideal paradigm should meet specific requirements. It should involve attention reorienting, while allowing the arousal level to fluctuate. An oddball paradigm is an appropriate option, for such tasks are of low difficulty by design, which allows the subjects’ mind to wander while maintaining high behavioral response accuracy. It therefore facilitates our examination of the internal arousal fluctuations and its interaction with the orienting and allocation of attention. In addition, as pupillometry was an important aspect of our study (as will be discussed below), we adopted an auditory instead of visual oddball paradigm to eliminate potential ocular related confounds.

With the experimental paradigm confirmed, the next logical question to ask is, what could serve as a quantitative measurement or index for arousal, and how could we retrieve information on the underlying neural processes? As we are working with non-clinical population, it is essential for us to capitalize on noninvasive imaging approaches to examine the neural processes of interest. Here
it is worthwhile to briefly introduce the biological structure of a neuron, and how it inspired our unique combination of measurements.

Neurons have three basic parts: 1) a cell body that contains the nucleus and most of the neuron’s metabolic machinery; 2) an axon that carries information to other cells via its synaptic endings; and 3) multiple dendrites that receive inputs from synapses with other nerve cells. Meanwhile, the transfer of information from one neuron to another is typically mediated by a variety of neurotransmitters. Therefore when neurons become active, this state of activation can be conveyed in three ways per the neuronal structure and mechanism of communication: 1) metabolism of neurons will increase as the cell body requires more energy; 2) electrical signal will be transmitted along neuronal axons by action potentials; and 3) neurotransmitters will be released by neurons to stimulate target neurons [Purves et al., 2012].

From the perspective of examining changes in neuronal metabolism to infer neural activity, we use functional magnetic resonance imaging (fMRI). As neuronal activity causes an increase in blood flow, the local blood oxygen subsequently experienced a relative surplus. The signal measured in fMRI depends on this change in oxygenation and is therefore referred to as the blood oxygenation level dependent (BOLD), signal [Poldrack et al., 2011].

From the perspective of examining transmitted electrical signal to study neural activity, we turn to electroencephalography (EEG) recordings. When synaptic input of a cortical area results in a voltage gradient, fluctuating voltages are generated. The electrode on the subject’s scalp detects the associated voltages from currents that propagated through the skull. These firings from active neurons are then reflected in the EEG recordings across different sites on the scalp [Purves et al., 2012].

While the characteristics of the reorienting system can be inferred from cortical neural activity measured with scalp EEG or fMRI, the anatomical location of the brainstem arousal system imposed a challenge on noninvasive recording of the internal arousal states. Nevertheless, mounting evidence has pointed towards a robust relationship between pupil size and LC-NE activity [Aston-Jones and Cohen, 2005, Gilzenrat et al., 2010]. Specifically, the presence of a relationship between LC-NE activity and task performance has since been shown in humans, using pupil dilation as a measure of LC-NE activity [Gilzenrat et al., 2010, Murphy et al., 2011, Eckstein et al., 2017]. Specifically, intermediate level of tonic LC activity was accompanied by phasic pupil dilation in response to
task-relevant stimuli, and were associated with better performance. Contrarily, both low and high levels of tonic LC activity were accompanied by a lack of phasic pupillary responses and diminished task performance [Corbetta et al., 2008, Murphy et al., 2011, Einhäuser, 2017, Eckstein et al., 2017]. These findings suggest that pupil diameter can serve as a reliable proxy for the level of arousal, consequently enabling the external measurements of the internal arousal states [Aston-Jones and Cohen, 2005, Murphy et al., 2011, Hong et al., 2014, Murphy et al., 2014].

1.3.1 Integration of pupillometry and neural measures

With the examination of internal arousal states enabled by pupillometry recording, a rich body of studies has been devoted to investigating the relationship between the reorienting and arousal systems in the recent years, with an increasing interest in concurrent cross modality analysis. In more specific terms, simultaneous pupillometry and scalp EEG studies investigated the poststimulus neural components that covaried with pupil-linked arousal [Murphy et al., 2011, Hong et al., 2014, Kamp and Donchin, 2015, van Kempen et al., 2019], with simultaneous scalp EEG and fMRI studies examining the spatial correlates of corresponding neural processes [Goldman et al., 2009, Walz et al., 2013, Walz et al., 2014], and simultaneous pupil and fMRI studies exploring the extent to which pupil-linked arousal is related with activities localized inside specific core regions of the LC-NE system [Murphy et al., 2014, Eckstein et al., 2017].

While this recent work has undoubtedly furthered our understanding of how the arousal system may interact with the reorienting system, the data integration approach has remained almost exclusively pairwise (if not making inferences by using a single modality). In other words, of all the three dominant physiological and neuroimaging recording modalities to infer activities of the arousal and reorienting systems, previous studies have largely used a selected combination of two (i.e. pupil and EEG, EEG and fMRI, or pupil and fMRI). A concurrent dual modality analysis, however, is likely to lack revealing power when compared with a simultaneous triple modality analysis, and may only be capable of revealing part of the true dynamics and interactions between the arousal and reorienting systems. Depending on the recruited modalities, such pairwise analysis will not be able to provide information in either a robust index of the level of arousal, accurate temporal resolution of the neural processes, or precise spatial resolution of the activated cortical or subcortical regions related to specific neural processes. For instance, a pupil-fMRI dual modality analysis could infer
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if the tonic or phasic level of pupil-linked arousal interacted with neural processes in certain brain regions, yet the slow responses of both measures would obstruct inferences on the exact timing of when such interaction might have taken place. One could argue that a meta-analysis holds the potential of fusing information across dual modality analysis, nevertheless the distinct differences in the experimental setup, subject experience, and data analysis could make such integration not well-suited for meaningful interpretation.

This dissertation addressed such limitations by concurrently recording and capitalizing on the unique information each of the three dominant modalities may contribute. Specifically, pupil diameter serves as an index for the level of internal arousal, with prestimulus baseline pupil diameter (PDB), indexing the baseline or tonic arousal, and stimulus driven poststimulus pupillary response (PR), indexing the evoked or phasic arousal. EEG and fMRI then provide complementary information on neural processes with fine temporal and spatial resolution, respectively. Taken together, our recordings of pupil, EEG, and fMRI data in an auditory oddball task enabled us to examine arousal and the underpinning neural activity from different perspectives, and facilitated the creation of a comprehensive mapping of the spatiotemporal dynamics and the dynamical interactions between the arousal and reorienting systems.

1.4 Innovative acquisition and analysis approaches

While the combination of the three modalities of data was by itself an advance, our study built on this innovative practice with two novel approaches, reflected in both the acquisition and analysis of the data.

The first novel aspect of our study was the concurrent recording of pupil, EEG, and fMRI. Data acquired in different sessions with similar experimental paradigm carry some major advantages, especially in the case of EEG-fMRI study (as EEG acquired inside the scanner is known to be susceptible to specific artifacts related to the scanner’s magnetic field) [Debener et al., 2006, Debener et al., 2009, Goldman et al., 2009]. Nevertheless, certain experimental confounds can only be overcome with simultaneous protocols [Jorge et al., 2014]. More importantly, the fundamental motivation behind this study was our interest in the trial-to-trial variabilities of the neural activity in an attention reorienting task, which simply cannot be achieved via non-concurrent recordings.
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The second novel aspect of this thesis was the utilization of single trial variability (STV) in carrying out analysis and making inferences of the data. This approach fell in line with our interest in endogenous fluctuations in the brain, and was reflective of our hypothesis that trial-to-trial variability was capable of explaining more variance across modalities, than conventional trial-averaged measures. Specifically, in the case of EEG data analysis, we used EEG signal from all electrodes and all trials to train a classifier that could maximally discriminate between neural responses under different task conditions (i.e. EEG signal evoked by a standard versus an oddball stimulus). In addition, this data driven approach was performed on various poststimulus time windows, and in essence created different “EEG discriminating components” which are capable of capturing the most task-relevant neural processes and their corresponding timings. Consequently, we used both pupillometry and EEG derived STVs (i.e. the EEG discriminating components at various poststimulus times) to inform combined analyses with fMRI data, as these STV measures could be better suited to explain the variability in the BOLD signal, therefore facilitating more informative mapping of spatial correlates to neural processes of interest.

1.5 Comprehensive mapping of dynamics

In light of the unique acquisition and analysis approach we used, our findings provide a comprehensive mapping of the spatiotemporal dynamics of attention reorienting and its interaction with the internal arousal states. Using pairwise modality analyses which correlate data of one modality to another, we identified neural correlates related to different levels of arousal, as well as brain regions that are linked to various temporally specific neural processes. We proceeded to examine the interactions between arousal and attention reorienting related neural processes at different poststimulus times, and were able to uncover brain regions where this interaction likely took place.

For clarity, throughout this thesis, references to attention imply the reorienting of attention, and references to arousal imply the pupil-linked arousal. With respect to EEG measures, “EEG components” refer to the poststimulus EEG discriminating components derived through a sliding window approach (which will be described in Chapter 4.1), with “EEG STV”, “EEG variability”, or “EEG component variability” referring to the STVs embedded in these EEG discriminating components. With respect to the structure of an experiment, time series of one continuous stream
of data are referred to as a “run” (or “scan” in the context of fMRI acquired data), and a set of multiple runs is referred to as a “session” [Monti, 2011]. Each subject undergoes multiple runs with brief interruptions in between, and each experiment consists of one concurrent pupil-EEG-fMRI session. Lastly, poststimulus times are divided into three distinct ranges to facilitate further discussion - 1) an early window range (0 to 325 ms poststimulus), 2) a middle window range (325 to 485 ms poststimulus), and 3) a late window range (485 to 800 ms poststimulus). This categorization is referred to as an “early window”, “middle window”, or “late window”, followed by the specific timing in ms.

Subsequently, we present an overview of the chapters -

Chapter 2 opens this dissertation with the critical first step: data acquisition. We discuss the acquisition procedures in two experiments: 1) an already published experiment which took place outside of the MR scanner, using simultaneous pupil and EEG recording [Hong et al., 2014]; and 2) the main focus of this thesis, a simultaneous pupil, EEG, and fMRI experiment which took place inside the scanner. The rest of the dissertation follows this branched structure - i.e. we will always introduce the simultaneous pupil-EEG experiment first, before moving on to discuss the simultaneous pupil-EEG-fMRI experiment.

Chapter 3 follows the data acquisition with a discussion on data pre-processing steps. Chapter 4 then summarizes the data analysis approaches performed in this thesis - namely, single trial EEG analysis, and general linear model (GLM) analysis.

Starting from Chapter 5, we begin to introduce the key findings of this study. Chapter 5 presents our results in connecting pupil-linked arousal to neural processes engaged in attention reorienting. We found that baseline pupil diameter correlates with EEG component variability at both an early (175 to 200 ms) and middle (350 to 400 ms) poststimulus time, suggesting a potential relationship between baseline arousal and evoked EEG responses.

Shifting from simultaneous pupil-EEG to a simultaneous pupil-EEG-fMRI experiment, Chapter 6, 7, 8, 9, 10 constitute the main focus of this dissertation, and are organized with respect to the number of modalities involved.

First, Chapter 6 summarizes the results from single modality analyses with trial-averaged pupil, EEG, and fMRI responses.
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From the perspective of linking arousal with neural processes at different poststimulus times, Chapter 7 commences the cross modality analyses with the combination of pupil and EEG data. This chapter performs an analysis similar to that in Chapter 5, although the results are not necessarily a replication of our previous findings. Specifically, we found that baseline pupil diameter exhibited a quadratic relationship with late window (475 to 525 ms) EEG variability, contrary to the previously negative linear relationship observed in the simultaneous pupil-EEG experiment. Additionally, pupillary response demonstrated a positive linear relationship with middle window (350 ms) EEG variability, suggesting for the first time that event-related pupil-linked arousal may be directly linked to neural processes happening at such poststimulus times.

Next, to identify spatial correlates of neural processes engaged throughout the task, Chapter 8 continues the pairwise modality analyses with the combination of EEG and fMRI data. Largely consistent with previous findings [Walz et al., 2013, Walz et al., 2014], we found that task-relevant regions are linked to early window (225 to 300 ms) and middle window (350 to 375 ms) EEG variability, while intrinsically-driven and executive-function related regions were correlated with middle window (375 to 425 ms) and late window (600 ms) EEG variability. These findings once again demonstrate the capability of trial-to-trial variability in linking both temporally and spatially specific neural components.

After investigating how pupil-linked arousal and temporally specific neural processes covary, and the spatial correlates of various EEG components in the previous chapters, Chapter 9 investigates the brain regions that are potentially correlated with different levels of pupil-linked arousal, with the combination of pupil and fMRI data. We discovered that baseline pupil-linked arousal was linked to regions in the prefrontal cortex, specifically the anterior cingulate cortex (ACC); whereas event-related pupil-linked arousal was more closely linked to regions in the parietal lobe, specifically the superior parietal lobule (SPL). To the best of our knowledge, these findings constitute some of the first evidence which differentiates brain regions correlated with baseline pupil-linked arousal apart from those correlated with event-related pupil-linked arousal in an attention reorienting task.

Taken together, findings from the dual modality analyses implied the following inferences - baseline pupil-linked arousal is temporally linked to late window (475 to 525 ms) EEG variability, and spatially linked to the prefrontal regions. Event-related pupil-linked arousal, on the other hand, is temporally related to middle window (350 ms) EEG variability, and spatially related to
task-relevant regions in both the dorsal and ventral attention networks. It is therefore tempting to conclude that the interaction between different levels of pupil-linked arousal and temporally specific neural components indeed took place in the regions observed above.

However, one of the subtleties of cross modality analyses, is the possibility that covariation in the pairwise modality analyses may point to neural activity of different sources. For instance, the fact that event-related pupil-linked arousal is linked to middle window (350 ms) EEG variability, and also linked to task-relevant regions does not provide sufficient evidence to conclude that the variability of event-related pupil-linked arousal interacts with neural processes around middle window (350 ms), and this interaction is expressed in task-relevant regions. It is possible that these two links simply stemmed from different pathways, and should therefore be treated independently. What additional information, or more specifically, what kind of multimodal integration, can then shed more light on where the interaction between pupil-linked arousal and neural processes might have taken place?

Chapter 10 aims to answer this question with preliminary results from fusing data across all three modalities. Contrary to pairwise modality analyses, which incorporated two modalities in the analyses, we discuss our approach in combining information from all three modalities to make inferences. The first triple modality analysis illustrates the additional inferences enabled by a complete combination of results from each dual modality analysis. Specifically, linkage between event-related pupillary response and middle window (350 ms) EEG variability may be expressed in task-relevant regions like the SPL and postcentral gyrus (PoCG). As event-related pupil-linked arousal is linked to middle window (350 ms) EEG variability, and to the regions above; while middle window (350 ms) EEG variability is also linked to the regions described above when analyzed independently. This finding suggests that phasic pupil-linked arousal and its interaction with event-related neural activity can be inferred both temporally and spatially.

In addition to the comparison approach we adopted in the first triple modality analysis, the second triple modality analysis creates a true interaction term with both pupil and EEG STV measures, before feeding this term in the regression analysis to inform BOLD correlates of such interaction. Our efforts uncovered that the interaction between baseline pupil-linked arousal and late window (525 ms) EEG variability is expressed in regions like the superior lateral occipital cortex (LOC), precuneus cortex (PCUN), and the middle frontal gyrus. More importantly, this relation-
ship cannot be inferred from dual modality analyses alone. In other words, using an interaction term which combines pupil and EEG variability achieves the tuning of the whole-brain analysis, and this combined variability is capable of identifying the locations which are correlated with the interactions between internal arousal states and neural processes involved in attention reorienting.

In summary, our work in this thesis provides a novel spatiotemporal mapping of both the dynamics of pupil-linked arousal and attention reorienting, and the dynamics of such interaction between the two systems. This is achieved by applying innovative approaches in both data acquisition and data analysis. Our findings provide additional evidence towards the mechanism and function of how human orients attention, and how arousal is linked to such seemingly trivial yet fundamentally critical cognitive function.
Chapter 2

Data acquisition

This chapter summarizes the major experimental setup and data acquisition methods we applied in this dissertation. We discuss the acquisition procedures for the two experiments that were performed. The first experiment was an already published study which took place outside of the MR scanner, using simultaneous pupil and EEG recording [Hong et al., 2014]. And the second experiment which is the main focus of this thesis, was a simultaneous pupil, EEG, and fMRI study which took place inside the scanner. The rest of the dissertation follows this branched structure - i.e. we will always introduce the simultaneous pupil-EEG experiment first, before moving on to discuss the simultaneous pupil-EEG-fMRI experiment.

2.1 Oddball paradigm

We used the classic auditory oddball paradigm for both experiments described in this dissertation. As we were interested in the intrinsic fluctuation in neural processes engaged in attention reorienting, the oddball paradigm seemed to be an appropriate option. This type of experiment requires the subject to respond to a series of unexpected yet behaviorally relevant stimuli [Corbetta et al., 2008], and is by design of low difficulty. This allows the subjects’ mind to wander while maintaining high behavioral response accuracy, and therefore facilitates our examination of endogenous fluctuations in neural processes of interest. In addition, as pupillometry was an important aspect of our study, we adopted an auditory instead of visual paradigm to eliminate potential ocular related confounds.

Specifically, we used an auditory paradigm with 80% of standard and 20% of oddball (target)
stimuli. The standard stimuli were pure tones with a frequency of 350 Hz, while the oddball stimuli were broadband (“laser gun”) sounds. Each stimulus lasted for 200 ms with an inter-trial interval (ITI) sampled from a uniform distribution between 2 s and 3 s. Subjects were instructed to respond with a button press as quickly and accurately as possible, once they heard the oddball sound.

2.2 Acquisition systems

2.2.1 Simultaneous pupil-EEG experiment

This study was carried out in accordance with the guidelines and approval of the Columbia University Institutional Review Board. Written informed consent was obtained from all participants prior to the experiment.

In the simultaneous pupil-EEG experiment which was conducted outside of the scanner, data acquisition was performed in a dark electro-magnetically shielded room, to control for visual sensory input (especially sudden luminance changes) that might affect the pupil diameter. Fifteen subjects (7 female; mean age 26.8 years, range = 20 to 44 years) participated in the experiment. One participant was excluded because of excessive artifacts in the EEG data. All participants had normal or corrected-to-normal vision and no history of psychiatric illness or head injury. Throughout the entire experiment, subjects’ pupil diameter was measured at a rate of 1 kHz with an EyeLink 1000 infrared eye-tracker (SR Research, Mississauga, ON, Canada). Subjects were instructed to fixate on a central white cross for the duration of each run. Subjects’ EEG was simultaneously recorded using a 64 scalp electrode ActiveTwo system with electrode layout following the 10/20 configuration, at a sampling rate of 2048 Hz.

2.2.2 Simultaneous pupil-EEG-fMRI experiment

This study was carried out in accordance with the guidelines and approval of the Columbia University Institutional Review Board. Written informed consent was obtained from all participants prior to the experiment.

While collecting data outside of the scanner has its own challenges, acquiring satisfactory multimodal data inside the scanner is particularly challenging due to the presence of a strong magnetic field created by the MR scanner, and its influence on the concurrently collected EEG [Debener
et al., 2009]. In the following section, we outline the specific approaches adopted in addressing these challenges.

Previous set up and transition to the current system

Pilot data was collected with a custom built MR-compatible EEG system inside a GE 3T scanner [Goldman et al., 2009, Sajda et al., 2010]. Although the custom-built system achieves reasonable data quality, it was unreliable and justified the need to transition to a new system. Consequently, we chose the BrainAmp MR system (Brain Products, Gilching, Germany), after a careful comparison of three different MR-compatible EEG recording systems (the custom built system, the most common commercial system (Brain Products, Gilching, Germany), and a prototype cap (g.Tec, Schiedlberg, Austria) that connects to the Brain Products amplifier and features a layer of reference electrodes isolated from the scalp) [Faller et al., 2017].

Challenges of recording inside the scanner

We address the challenges of concurrent pupil, EEG, and fMRI data acquisition inside the scanner from three perspectives: ensuring 1) the safety of participants, 2) the signal to noise ratio (SNR), and 3) the synchronization of stimuli/events.

**Ensuring subject safety** The main safety related risk during combined EEG-fMRI measurements is an increase in temperature of the EEG components, cables, electrodes and sensors that are connected to or come into contact with the test subject [Brain-Products, 2019]. As the strong magnetic fields and radio frequency pulses (when the scanner is on) would interact with the EEG recording system, this potential hazard calls for extremely careful planning in the experimental setup beforehand [Brain-Products, 2019].

In the simultaneous pupil-EEG-fMRI experiment, subject safety was ensured by complying with the recommended configurations outlined by the manufacturer of the EEG amplifier, Brain Products [Brain-Products, 2019]. These included but were not limited to MR sequence design with inherently low specific absorption rate (SAR) [Brain-Products, 2019], appropriate coil configuration and safe positioning of EEG cables inside the bore. Figure 2.1 demonstrates one of the practices described above - by using Siemens’ 64 channel coil which has a specifically designed rear port, the
Figure 2.1: Specifically designed rear port for simultaneous EEG-fMRI acquisition in a Siemens coil. Siemens, 3T Prisma, 64 channel coil with Brain Products cap [Siemens, 2013]. Image Copyright © 2019 Siemens Medical Solutions USA, Inc.

EEG cables could be directed from the subject to the amplifier without forming a loop [Siemens, 2013].

Ensuring event synchronization As the neural responses of interest happen on millisecond scale, accurate and stable synchronization between recording modalities is crucial. Proper synchronization between EEG recording and MR imaging was ensured via Brain Products’ SyncBox. The SyncBox receives pulses coming from the scanner’s gradient clock board directly, and can therefore synchronize the sampling rate of the amplifier with the scanner clock system [Brain-Products, 2019]. Meanwhile, synchronization between EEG and pupillometry recording was reinforced via an ethernet cable between the paradigm computer and the eye tracker. Figure 2.2 illustrates the overall schematic design of the recording system, with blue italic font highlighting the flow of
Figure 2.2: Hardware configuration. Schematic for simultaneous pupil-EEG-fMRI recording. Shown are various types of cables facilitating connection and synchronization between devices. Such cables include parallel port or line print terminal (LPT) cable, universal serial bus (USB) cable, Bayonet Neill–Concelman (BNC) cable, fiber optic (FO) cable, as well as other auxiliary, trigger, and Ethernet cables.

Ensuring high SNR  Even after subject safety and event synchronization were ensured, the specific recording environment of the MR scanner was still one of the greatest challenges. Data acquisition performed in and out of the scanner are fundamentally different, as illustrated by Tables 2.1 and 2.2.

Given the particular challenges for data acquisition in the MR environment, additional effort was invested to reduce measurement related noise. Specifically, we 1) created a custom rack for the eye tracker, to ensure that the tracker would not be obstructed by the stacked EEG amplifiers; 2) specified EEG amplifier settings to make sure that data saturation would not happen (exact
### CHAPTER 2. DATA ACQUISITION

<table>
<thead>
<tr>
<th>Pupillometry recording inside the MR scanner (with simultaneous EEG)</th>
<th>Pupillometry recording in a lab (with simultaneous EEG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracking remotely, subject’s pupil far from the tracker</td>
<td>Tracking locally, subject’s pupil close to the tracker</td>
</tr>
<tr>
<td>Potential obstruction from the EEG amplifiers (stacked by the subject’s head on the scanner bed)</td>
<td>No obstruction for the camera to locate the pupil</td>
</tr>
<tr>
<td>Potential vibration of the scanner bed and hence tracking target</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Table 2.1: Differences in pupillometry recording in an MR environment vs. in a non-MR environment setting.**

<table>
<thead>
<tr>
<th>EEG recording inside the scanner</th>
<th>EEG recording in a lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient artifact introduced by the scanner</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Potential amplifier saturation given large gradient artifacts</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cardioballistic artifact</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Potential electrical noise caused by the helium pump and the air conditioning in the scanner bore</td>
<td>No electrical noise (if inside a Faraday’s cage)</td>
</tr>
<tr>
<td>Potential interference in signal caused by vibration of the scanner transmitted to the amplifier</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Table 2.2: Differences in EEG measurements in an MR environment vs. in a non-MR environment setting.**
settings to be found in subsequent section); 3) performed real time gradient artifact cancellation on EEG data to enable online detection of abnormal signal, using RecView software by Brain Products (note that such gradient artifact cancellation was for visualization and quality control purposes only. Actual gradient artifact removal was performed on the raw data post hoc, as will be discussed in Chapter 3).

Data acquisition for the simultaneous pupil-EEG-fMRI experiment

Here we also demonstrates the adjustments made in experimental design in the simultaneous pupil-EEG-fMRI experiment, compared with the previous experiment. These changes were necessary to better control for both experimental and physiological confounds that were either not applicable or do not typically need to be controlled in the previous setting.

Experimental design  A total of 25 subjects were scanned and 6 were excluded from further analysis - 2 were rejected due to missing neuroimaging data, 2 were rejected due to abnormality in collected neuroimaging data, 1 was rejected due to excessive movement, 1 was rejected due to drowsiness and inability to complete the task as per instruction. For the 19 remaining subjects included in this study, 6 were male. Age ranged from 18 to 32 years old, with a mean of 25.9 years old and a standard deviation of 3.6 years. All participants had normal or corrected-to-normal vision and no history of psychiatric illness or head injury. An auditory oddball paradigm with 80% standard and 20% oddball (target) stimuli was used (as described in Section 2.1). Subjects were first familiarized with the task through a short version of the paradigm outside of the scanner. When inside the scanner, they were instructed to maintain their fixation on the screen to a fixation target, and to press a button on a gamepad with their right index finger as quickly and accurately as possible when they heard the oddball sound.

Every subject was scheduled to complete five runs in total (on average, subjects completed 4.7 runs, with a range of 3 to 5, and a standard deviation of 0.7 runs). Subjects were allowed to rest in between runs. Each run consisted of 105 trials, with a jittered ITI sampled from a uniform distribution between 2 s and 3 s. Each session was therefore completed in an average of 30 minutes.

There were two constraints imposed upon the otherwise randomized trial order - 1) the first five trials were always standards, and 2) there were no consecutive oddball trials, i.e. the inter-
oddball interval were controlled to be always larger than 4 s. These two constraints ensured that
the subjects were settled into the experiment before the first oddball trial appeared, and there was
enough time for the subject’s pupil diameter to go back to baseline before the onset of another
oddball trial.

The paradigm was presented via back projection with PsychToolbox (PTB, Version 3.0.12) in
MATLAB (The Mathworks, Natick, MA, USA), with the stimuli delivered to subjects via ear-
phones. Synchronization was achieved with a combination of parallel port, USB connection and
ethernet cables, as illustrated in Figure 2.2. Throughout the experiment, there was a fixation tar-
get presented on a gray background, upon which the subjects were instructed to maintain a stable
fixation. The fixation target resembled a combination of bulls eye and cross hair, which had been
demonstrated to result in low dispersion and microsaccade rate among other alternatives [Thaler
et al., 2013].

Pupillometry  Pupillometry recording was performed with an MR-compatible EyeLink 1000 Plus
in Long Range Mount, at a sampling rate of 1 kHz. For each subject, the position of the EEG
amplifiers was adjusted so that it did not obstruct line of sight from the eye tracker to the subject’s
eyes (as the amplifiers were stacked at the end of the bore and directly in front of the eye tracker,
as illustrated in Figures 2.3 and 2.4). Before the experiment, calibration was also performed to
ensure that the eye tracker was able to track the position of the subject’s pupil accurately.

EEG  EEG was recorded with a 64 channel Brain Products BrainAmp MR Plus system, at a
sampling rate of 5 kHz. The 64 channels include 63 cap electrodes and 1 electrocardiogram (ECG)
electrode. Inside the scanner, sandbags were used to stabilize the amplifiers against any potential
vibrations caused by the scanner. As we used Siemens’ 64 channel coil, which has a specifically
designed rear port that could directly route the EEG cables from the subject to the amplifier (Figure
2.1), the potential disruption caused by the EEG cable to the MR images were also minimized.
In addition, in order to avoid amplifier saturation and ensure high SNR, we used the following
specifications in the Brain Products Recorder environment: 1) voltage resolution at 0.5 uV, 2) low
cut-off frequency at 0.1 Hz, 3) high cut-off frequency at 250 Hz, and 4) all electrodes’ impedances
were controlled under 20 kOhm.
Figure 2.3: MR-compatible EEG system setup inside the scanner. Illustration of Brain Products EEG system setup inside the scanner [Brain-Products, 2018]. Image Copyright © Brain Products GmbH.
Figure 2.4: MR-compatible eyetracking system setup inside the scanner. Illustration of the position of the long range mount eye tracker inside the scanner. The view corresponds to looking down the scanner bore, from front (where subject enters head forward) to back. [SR-Research, 2018]. Image Copyright © 2019 SR Research Ltd.
fMRI MR data was recorded inside a 3T Siemens Prisma scanner, with a 64 channel head/neck coil. Four types of images were collected for each subject. Specifically:

- Structural T1 image (MPRAGE) was collected with an echo time (TE) of 3.95 ms, a repetition time (TR) of 2300 ms, a flip angle of 9 degrees (FA), and an acquisition time of 9.46 minutes. In-plane resolution was 1 mm, with a slice thickness of 1 mm, a field of view (FOV) of 176 mm x 248 mm (176 x 248 voxels), a total of 256 axial slices, and a left to right (L/R) phase encoding direction.

- Functional Echo Planar Imaging (EPI) images were collected with a TE of 25 ms, a TR of 2100 ms, an FA of 77 degrees, and an acquisition time of 5.25 minutes per run (i.e., 150 volumes). In-plane resolution was 3 mm, with a slice thickness of 3 mm, an FOV of 192 mm x 192 mm (64 x 64 voxels), a total of 42 axial slices, an anterior to posterior (A/P) phase encoding direction, and an even interleaved ascending order.

- One single-volume high resolution EPI image was collected with a TE of 30 ms, a TR of 6000 ms, an FA of 90 degrees, and an acquisition time of 9.5 minutes. In-plane resolution was 2 mm, with a slice thickness of 3 mm, an FOV of 192 mm x 192 mm (96 x 96 voxels), a total of 42 axial slices, and an A/P phase encoding direction.

- T1 turbo-spin-echo (TSE) images were collected with a TE of 14 ms, a TR of 600 ms, an FA of 90 degrees, and an acquisition time of 12.5 minutes. In-plane resolution was 0.4 mm, with a slice thickness of 3 mm, an FOV of 166 mm x 205 mm (416 x 512 voxels), a total of 10 axial slices, and a L/R phase encoding direction.

The single-volume high resolution EPI and structural T1 images were collected before the task started, and acquired for registration purposes. Functional EPI images were collected during the task. In addition, T1-TSE images were collected on a different session (during which the subject were not wearing the EEG cap), as the SAR of that pulse sequence was not compatible with the EEG cap. The T1-TSE images were acquired for localizing the LC, as demonstrated in previous publications [Keren et al., 2009, Murphy et al., 2014].

A preliminary quality assurance (QA) test was carried out on all functional EPI images with a utility gear on the platform Flywheel [Flywheel, 2018], which generated QA metrics such as
CHAPTER 2. DATA ACQUISITION

We assessed the acquired images’ SNR, visually inspected the per slice variation, and mean image. This QA was performed for a first assessment of data quality of every newly collected data set.

[Flywheel, 2018]
Chapter 3

Data pre-processing

This chapter discusses the data pre-processing and analysis approaches used in this dissertation. Similar to Chapter 2, we first introduce the approaches utilized in the previously published simultaneous pupil-EEG experiment in Section 3.1.1, before focusing on the simultaneous pupil-EEG-fMRI experiment starting from Section 3.1.2.

3.1 Data pre-processing

3.1.1 Simultaneous pupil-EEG experiment

Pupillometry data pre-processing

For continuous pupil diameter data, periods of blinks were detected using Eyelink’s on-line parsing system, and then linearly interpolated in MATLAB. In order to compare within and across subjects, the pupil trace for each trial was normalized to the mean pupil diameter of the corresponding subject, resulting in a percentage pupil diameter change.

EEG data pre-processing

For continuous EEG data, a 0.5 Hz high-pass filter was used to remove low frequency noise, and 60 Hz and 120 Hz notch filters were used to remove electrical line noise. The EEG data were then re-referenced as per the common average reference scheme [Ludwig et al., 2009]. An anti-aliasing filter was applied and the data were then down-sampled to 1 kHz to match the sampling rate of
the pupil data.

**Epoching of pre-processed pupillometry and EEG data**

EEG and pupil diameter data were epoched identically, from 1 s prior to 2 s following each stimulus, with baseline removal on the last 500 ms prior to stimulus onset. Trials with either excessive noise in the EEG or pupillary data were manually identified and removed. Similarly, trials that resulted in behavioral error (i.e. missed oddballs or incorrectly responded to standards) were excluded from subsequent analyses. Oddball trials where the preceding trial was also of type oddball were rejected, since it was possible for the evoked pupil response of the first oddball trial to confound the pupil diameter baseline of the following trial.

### 3.1.2 Simultaneous pupil-EEG-fMRI experiment

While pre-processing for simultaneously collected pupil-EEG data was relatively straightforward, it was inevitably more convoluted for simultaneously collected pupil-EEG-fMRI data. As previously discussed in Section 2.2.2 and illustrated in Tables 2.1 and 2.2, pupillometry and EEG data collected inside the scanner were more susceptible to MR environment related artifacts. The raw signal therefore calls for a careful and delicate data pre-processing approach - as too little pre-processing will not be able to treat the noise properly and uncover the real underlying signal; whereas too much pre-processing entails the danger of removing desired neural responses.

Here we also demonstrate the adjustments we made in data pre-processing steps in the simultaneous pupil-EEG-fMRI experiment, compared with the previous experiment. These changes were performed to better control for potential confounds related with the recording environment of the MR scanner.

**Pupillometry data pre-processing**

A similar pre-processing approach as described in [Urai et al., 2017] was adopted. Blinks detected by the Eyelink software were padded by 150 ms, then linearly interpolated. A peak detection algorithm were then used to remove additional blinks (peaks defined by samples larger than three standard deviations from the mean).
As the raw pupil data was recorded in units of area, the pupil area data was converted to pupil diameter based on the following formula provided by the eye tracker manufacturer:

\[\text{pupil diameter} = 256 \times \sqrt{\frac{\text{pupil area}}{\pi}}\]  

(3.1)

The pupil diameter time series were then bandpassed from 0.01 Hz to 10 Hz, with a second-order Butterworth filter, z-scored per run, and down-sampled to 500 Hz to match the sampling rate of the pre-processed EEG data.

**EEG data pre-processing**

**Gradient artifact removal** The most prominent source of noise in raw EEG data collected inside the scanner is the gradient artifact. During fMRI acquisition, the magnetic field inside the scanner changes over time due to the application of time-varying magnetic field gradients [Allen et al., 2000, Niazy et al., 2005, Abreu et al., 2018]. According to Faraday’s law of induction, these will induce an electromotive force within the conducting loop formed by the EEG hardware (electrodes, wires and amplification system). A spurious voltage is hence generated on the EEG electrodes which is usually called gradient artifact (GA) or imaging artifact [Allen et al., 2000, Niazy et al., 2005, Grouiller et al., 2007, Abreu et al., 2018]. If not removed or at least suppressed, the gradient artifact would mask all of the EEG signal due to the artifact’s high amplitude, as shown in Figure 3.1.

However, the gradient artifact’s perfect predictability means that it can be removed relatively effectively from the raw EEG signal [Debener et al., 2009]. Specifically, a gradient artifact removal in Brain Products’ Analyzer2 data processing software was carried out. Before the initial artifact removal, the raw EEG data was first visually inspected to ensure that the signal was not contaminated by other confounds. Such visual inspections include but were not limited to TR volume jitter and data saturation check, as any jitter in the TR volume or data saturation would result in unsatisfactory gradient artifact removal.

An average artifact template subtraction approach was then used to remove the GA artifact. Due to the GA’s strong deterministic component, this approach allows the artifact templates to be derived for each occurrence by averaging across multiple fMRI slice or volume epochs, before subtracting the averaged artifact template from the EEG signal [Allen et al., 2000, Abreu et al., 2018].
The specific algorithm implemented in Analyzer2 software took the 10 volumes before and after the volume of interest to generate a template, which was then subtracted to remove the common gradient artifact from the volume of interest. The data was then down-sampled to 500 Hz before undergoing further pre-processing.

**Ballistocardiogram artifact removal** Another significant source of noise in raw EEG data collected inside the scanner is the ballistocardiogram artifact (BCG). The BCG artifact is related to the cardiac cycle and scales in amplitude proportionally with the magnetic field strength [Herrmann and Debener, 2008, Debener et al., 2008, Tenforde et al., 1983]. Although the exact cause of the BCG artifact is still being investigated, it has been known to be induced by the small involuntary cardiac-related body movements (ballistocardiogram) [Debener et al., 2009]. Blood, EEG electrodes and EEG leads are all conductive, and the movement of conductive material in a high static magnetic field therefore creates a current that is picked up by the EEG [Herrmann and Debener, 2008, Debener et al., 2008, Debener et al., 2009]. The pulse artifact is clearly visible on EEG recorded inside the MR scanner even in the absence of scanning, and contributes amplitudes and frequencies that are close to the range of the usual EEG signal, with an amplitude that is on the order of 50 $\mu$V (at 1.5 T) and has a resemblance to epileptic spikes [Debener et al., 2009]. Figure 3.2 shows an illustration of the BCG artifact.

Before BCG removal, a 10th order median filter was first applied to the EEG data where the GA had been removed, to reject any residual gradient artifact. A 4th order bandpass Butterworth filter was then applied from 0.5 Hz to 50 Hz, to remove DC drift and high frequency noise. Each subject’s filtered EEG data were then concatenated over runs before the application of BCG removal. Since the occurrences of BCG artifact are approximately time-locked with the cardiac cycle, an average artifact template subtraction algorithm can be used, similarly to when correcting for the GA [Abreu et al., 2018]. Specifically, QRS detection and subsequent BCG removal were carried out with EEGLAB’s FMRIB plugin, using the simple mean approach. This approach was relatively conservative in artifact removal as it simply averaged successive pulse artifacts around a contaminated data segment before subtracting the result from the data. The BCG removed data were then re-referenced to the common average, in preparation for further steps of pre-processing.
Figure 3.1: Gradient artifact. Illustration of the gradient artifact (GA) generated by a 2D multi-slice EPI sequence. (Top) 5 s traces of raw EEG data from 10 channels. At approximately 15 s, the fMRI acquisition starts, completely obscuring any neuronal activity being recorded. (Bottom) The zoomed red box shows the high-amplitude electrical potentials generated by the time-varying gradients applied during the acquisition of four image slices using 2D multi-slice EPI. Reprinted by permission from Frontiers: Frontiers in Human Neuroscience, [Abreu et al., 2018], Copyright © 2018 Abreu, Leal and Figueiredo.
Figure 3.2: BCG artifact. Example of the pulse artifact in ongoing EEG data recorded in a 1.5 T MRI scanner without MRI scanning. EEG traces at lateral sites over the left and right hemispheres, where the artifact is usually most pronounced, are shown. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, [Debener et al., 2009], Copyright © 2009 Springer-Verlag Berlin Heidelberg.
**Blink artifact removal** The final stage of artifact rejection was performed using independent component analysis (ICA), to remove eye blinks specifically. ICA has been demonstrated to have the capability of effectively removing blink related artifacts from EEG recordings, especially when compared with simple regression based methods (where the practice of regressing out eye movement or blink related activity usually involves subtracting a portion of the relevant EEG signal as well) [Makeig et al., 1996, Jung et al., 1998a, Jung et al., 1998b, Jung et al., 1999, Jung et al., 2000a, Jung et al., 2000b]. Specifically, we used EEGLAB’s ICA function to compute ICs, before manually identifying and removing the blink IC (which usually resides over frontal electrodes and have characteristic activations [Jung et al., 2000a, Jung et al., 2000b]).

**Epoching of pre-processed pupil and EEG data**

EEG and pupil diameter data were epoched identically, from 0.5 s prior to the stimulus to 2 s following each stimulus. Only EEG epochs were baseline removed on the last 500 ms prior to stimulus onset. Trial rejection was carried out with a probability distribution based criteria (trials within which the data for a single channel was outside of 6 times of the standard deviation (s.d.), and within which the data for all channels was outside of 2 s.d. in terms of probability were rejected). Trials during which subjects responded incorrectly, or failed to respond were also rejected.

**fMRI data pre-processing**

The fMRI data pre-processing was carried out using FMRI Expert Analysis Tool (FEAT) Version 6.00, part of FMRIB Software Library (FSL) [FMRIB, 2018]. Bias field correction on all images were performed with FMRIB’s Automated Segmentation Tool (FAST). FAST segments a 3D image of the brain into different tissue types, whilst also correcting for spatial intensity variations, also known as bias field [Zhang et al., 2001]. The underlying method is based on a hidden Markov random field (MRF) model and an associated expectation-maximization algorithm [Zhang et al., 2001]. In specific terms, the parameters used for bias field correction were: 1) three classes of tissue-types, 2) MRF beta value for main segmentation phase of 0.1, 3) six main-loop iterations during bias-field removal, and 4) 20 mm of bias field smoothing extent (FWHM).

After bias field correction, brain extraction was carried out with Brain Extraction Tool (BET) in FSL [FMRIB, 2018, Smith, 2002, Jenkinson et al., 2005]. We used 1) a fractional intensity
Lastly, registration of the functional data to the high resolution structural image was carried out using the boundary based registration [Greve and Fischl, 2009]. Registration of the high resolution structural to standard space images was carried out using FMRIB’s Linear Image Registration Tool (FLIRT) [Jenkinson and Smith, 2001, Jenkinson et al., 2002] and was then further refined using FMRIB’s Nonlinear Image Registration Tool (FNIRT) [Andersson et al., 2007a, Andersson et al., 2007b]. Specifically, 1) motion correction was performed using MCFLIRT [Jenkinson et al., 2002], 2) slice-timing correction was performed using Fourier-space time-series phase-shifting, 3) spatial smoothing was performed using a Gaussian kernel of FWHM 5 mm, 4) grand-mean intensity normalization of the entire 4D dataset was performed by a single multiplicative factor, and 5) highpass temporal filtering was performed with a Gaussian-weighted least-squares straight line fitting, with $\sigma = 50$ s.
CHAPTER 4. DATA ANALYSIS

Chapter 4

Data analysis

The following chapter describes the data analysis approaches used in this dissertation. While the specific analyses may differ from experiment to experiment, the two main analyses we conducted were single trial EEG analysis and general linear model (GLM) analysis, which will be introduced first (in Sections 4.1 and 4.2, respectively). These two analysis approaches served as the foundation for all subsequent cross modality analyses.

Additionally, the rest of the sections in this chapter are organized with respect to the number of modalities involved. We will start with analysis that used a single modality, followed by analyses based on dual (pairwise) modalities. In the context of this thesis, dual or pairwise modality analysis investigates the relationship between two modalities of data, typically by using information from one modality to inform another. For the simultaneous pupil-EEG-fMRI experiment specifically, we will discuss triple modality analyses which integrates data from all three modalities to make inferences.

4.1 Single trial EEG analysis

4.1.1 Motivation

Traditionally, it is not uncommon to sacrifice certain aspects of the information contained in the data, to achieve satisfactory signal to noise ratio. In the context of EEG data analysis, the method of averaging across trials, as used in the event related potentials (ERP) approach, is one such example. While this approach holds certain merits, it precludes other types of analyses like those
CHAPTER 4. DATA ANALYSIS

based on trial-to-trial variability. This type of STV, however, can lead to increased statistical power and may encode important endogenous fluctuations associated with specific neural processes [Gerson et al., 2005, Parra et al., 2005, Goldman et al., 2009]. Moreover, as ERPs are typically confined to specific time periods after a stimulus onset, the less defined time periods could therefore remain under-examined.

To address the limitations of ERPs, we performed a single trial analysis which collapsed information across electrodes instead of trials. In more concrete terms, our algorithm used signal from all channels to create a classifier that could maximally discriminate the neural signal between different task conditions. Specifically, we used a sliding window logistic regression method described in [Parra et al., 2005, Sajda et al., 2009, Sajda et al., 2010]. With this technique, we were able to extract an EEG discriminating component which can be examined at specific times across the entire trial, and therefore facilitated the tracking of temporal progression of task related neural activity at the time resolution of the EEG. In other words, the STV of this EEG discriminating component not only preserves the trial-to-trial variability of interest, but is also indicative of the most task-relevant neural processes and their corresponding timing.

4.1.2 Sliding window technique

A sliding window technique as described in [Parra et al., 2005, Sajda et al., 2009, Sajda et al., 2010] was used. Specifically, with $x(t)$ denoted as the vector of multidimensional EEG data at time $t$ within a short time window, a weighting vector, $w$, was selected to generate a projection, $y(t)$, of the EEG signal so that $y(t)$ can achieve maximal discrimination between oddball and standard trials.

In more concrete terms, a time window and its center, $\tau$, were first determined. All time windows had a width of $D = 50$ ms and the window center, $\tau$, was shifted from 0 ms to 1000 ms relative to stimulus onset, in 25 ms increments. The EEG signal of all trials within that window, $x_i(t)$, were then extracted and served as the input to a logistic regression algorithm to train a classifier to discriminate the EEG responses of oddball from standard trials. Here $x_i(t)$ is a matrix with a size of $N \times (D' \times T)$, where $N$ is the number of EEG channels, $D'$ is the number of samples in one training window (i.e., $D' = D \times$ sampling rate of EEG/1000 ms), and $T$ is the total number of trials, with $i = \{1...T\}$ indexing the trials.
The assumption in logistic regression is that projections of the data, \( y = w^T x \), is distributed according to a logistic function (with superscript “\( T \)” in subsequent text denoting the transposed matrix), i.e., the likelihood that sample \( x(t) \) belongs to the class of positive examples, \( c = +1 \), follows:

\[
p(c = +1 | x) = f(y) = \frac{1}{1 + e^{-y}} = \frac{1}{1 + e^{-(w^T x)}} \tag{4.1}
\]

Similarly, the likelihood for negative examples, \( p(c = -1| x) = 1 - f(y) \), also follows the logistic function [Parra et al., 2005]. Translated to the EEG data \( x_i(t) \), and subsequent projections of the data, \( y_i(t) \), in one training window \( \tau \), logistic regression was then used to maximize the likelihood of the data with respect to the model parameters, i.e., the weighting vector, \( w(\tau) \):

\[
w(\tau) = -\arg \min_w L(w(\tau)) = -\arg \min_w \sum_{i=1}^{T} \log p(c_i(t)|y_i(t)) \tag{4.2}
\]

Here, \( y_i(t) \) is a row vector with a length of \( D' \times T \), and \( w(\tau) \) is a column vector with a length of \( N \) [Parra et al., 2005]. A corresponding forward model, \( a(\tau) \), can then be found by linearly predicting \( x_i(t) \) from \( y_i(t) \), with signal at time points within the specific training window \( \tau \):

\[
a(\tau) = \frac{x_i(t)y_i(t)}{y_i(t)^T y_i(t)} \tag{4.3}
\]

These forward models at different training window centers can be viewed as scalp plots and interpreted as the correlation between the discriminating components and the observed EEG [Gerson et al., 2005, Parra et al., 2005, Goldman et al., 2009, Sajda et al., 2009, Sajda et al., 2010]. Figure 4.1 illustrates this sliding window technique.

Additionally, in order to control for noise, an average of \( y_i(t) \) within each time window \( \tau \) was computed, arriving at \( y_i(\tau) \), a row vector with a length of \( T \). The transformation of EEG signal within one training window to its projection can then be expressed as:

\[
y_i(\tau) = \frac{1}{D} \sum_{t=\tau-rac{D}{2}}^{\tau+rac{D}{2}} w(\tau)^T x_i(t) \tag{4.4}
\]
\( y_i(\tau) \), termed the EEG discriminating component or EEG component in short, therefore captures the confidence of the classifier for each trial at each training window. The classifier’s performance, termed \( A_z \), was then estimated at different window centers by computing the area under the receiver operating characteristic (ROC) curve using a leave-one-out cross validation procedure [Green and Swets, 1988, Parra et al., 2005]. The significance level of \( A_z \) was determined by first performing the leave-one-out test after randomly permuting the trial labels, and repeating this permutation method 100 times for each subject. A null distribution of \( A_z \) values across the subjects were then constructed, and subsequently used to determine the \( A_z \) value of \( p < 0.01 \) threshold.

### 4.2 General linear model and statistical analysis

We used the general linear model to examine the relationship between our measures of interest. The independent variables could be behavioral, pupillary, or EEG measures, while the dependent variable could be EEG, or BOLD response measured through fMRI. In the simultaneous pupil-EEG experiment, the construction of GLMs using behavioral, pupillometry, and EEG data were relatively intuitive. In the simultaneous pupil-EEG-fMRI experiment, however, the sluggish temporal nature of the BOLD signal called for a slightly different model specification approach. Consequently, we will first discuss the common analyses used in both experiments in Sections 4.2, before providing more details on GLM based analysis used in the simultaneous pupil-EEG and pupil-EEG-fMRI experiment in Sections 4.3 and 4.4, respectively.

#### 4.2.1 General linear model

In general, GLM analysis is often performed in two steps: a single-subject analysis with data from each individual subject, followed by a multiple-subject analysis in which results from multiple subjects are combined on a group-level [Monti, 2011]. The dependent variable is modeled as a weighted sum of one or more known predictor variables (also called explanatory or independent variables), and the aim of the GLM is to estimate if, and to what extent, each predictor contributes to the variability observed in the dependent variable [Monti, 2011].

[Penny et al., 2007, Monti, 2011, Poline and Brett, 2012] offered excellent backgrounds and rationales behind the GLM analysis commonly used in cognitive neuroscience (with an emphasis
Figure 4.1: Sliding window technique. (I) Onset of standard (green) and oddball (pink) stimuli. (II) Specific temporal window used for EEG signal extraction with the duration of the window represented by the vertical shaded regions. (III) Logistic regression used to create the EEG discriminating component. Specifically, the goal of this sliding window technique is to find a projection, \( y_i \), of the multidimensional EEG signal, \( x_i \), within a short time window that achieves maximal discrimination between oddball and standard trials. All time windows had a width of \( D = 50 \text{ ms} \) and the window center, \( \tau \), was shifted from 0 ms to 1000 ms relative to stimulus onset, in 25 ms increments.
on modeling the BOLD response). The aim of the following text is to provide a brief overview of the GLM analysis used in this thesis, while additional and typically more technical details are accessible through [Penny et al., 2007, Monti, 2011, Poline and Brett, 2012].

**Single-subject analysis**

For a single subject, a dependent variable, $y$, of $n$ samples, can be modeled as the sum of $p$ predictor variables, $x_1...x_p$, each scaled by a parameter $\beta_1...\beta_p$:

\[
y_1 = x_{1,1} \beta_1 + x_{1,2} \beta_2 + \ldots + x_{1,p} \beta_p + \epsilon_1
\]

\[
y_2 = x_{2,1} \beta_1 + x_{2,2} \beta_2 + \ldots + x_{2,p} \beta_p + \epsilon_2
\]

\[
\vdots
\]

\[
y_n = x_{n,1} \beta_1 + x_{n,2} \beta_2 + \ldots + x_{n,p} \beta_p + \epsilon_n
\]

This relationship between the predictors and the observations can be re-written in matrix form with:

\[
Y = X \beta + \epsilon \quad (4.5)
\]

Here $Y$ is an $n \times 1$ column vector, $X$ is an $n \times p$ design matrix, with each column representing a different predictor variable. Additionally, $\beta$ is a $p \times 1$ vector containing the parameters, and $\epsilon$ is an $n \times 1$ vector containing the error values associated with each observation of $Y$ (i.e., the value of each observation that is not explained by the weighted sum of predictor variables) [Monti, 2011].

The ordinary least squares (OLS) method can be used to estimate the unknown $\beta$, and to determine if a given predictor variable significantly contributes to the changes in $Y$ [Monti, 2011]. With the criteria of OLS, the optimal parameters therefore should minimize the sum of squared errors:
CHAPTER 4. DATA ANALYSIS

\[ \text{Sum of squared errors} = \sum_{i=1}^{n} (\hat{Y}_j - X_j\hat{\beta})^2 \] (4.6)

\( \hat{Y}_j \) is the estimated dependent variable for the \( j^{th} \) observation using the computed parameter estimate \( \hat{\beta} \), and \( X_j \) is the \( j^{th} \) row in \( X \) corresponding to the specific sample of \( Y_j \). The parameter estimate \( \hat{\beta} \) also has the following characteristics:

\[ \hat{\beta} = (X^TX)^{-1}X^TY, \quad \text{var}(\hat{\beta}) = \sigma^2(X^TX)^{-1} \] (4.7)

**Multiple-subject analysis**

**Fixed effect analysis** Once single-subject data has been analyzed for a set of participants, individual results are aggregated to assess commonality and stability of effects within groups of interest [Holmes and Friston, 1998, Worsley et al., 2002, Monti, 2011]. One type of group analyses, termed the fixed effects (FFX) analysis, considers the magnitude of the effect from each subject to be fixed. FFX analyses thus represent the population variance as being a sole function of within-subject variability divided by the produce of subjects \( (N) \) and number of observations per subject \( (n) \) [Penny et al., 2007, Monti, 2011]. If one were to model the dependent variable \( y_{i,j} \) for trial \( j \) of subject \( i \), this observation can be formulated as:

\[ y_{i,j} = m_i + e_{i,j} \] (4.8)

The mean effect of each subject is \( m_i \), and the within-subject error \( e_{i,j} \) has zero mean and variance \( \text{var}[e_{i,j}] = \sigma^2_w \). The maximum-likelihood estimate for the mean effect and its variance of a single subject can then be expressed as:

\[ \hat{m}_i = \frac{1}{n} \sum_{j=1}^{n} y_{i,j}, \quad \text{var}(\hat{m}_i) = \frac{\sigma^2_w}{n} \] (4.9)

As discussed above, in an FFX analysis, \( \sigma^2_w \) is assumed to be the same for all subjects, and the error terms are assumed to be independent over subjects [Penny et al., 2007]. The estimate for the group mean and its variance are then:
\[
\hat{m}_g = \frac{1}{N} \sum_{i=1}^{N} \hat{m}_i, \quad \text{var}(\hat{m}_g) = \frac{\sigma^2_w}{Nn}
\] (4.10)

Another way to visualize the formulation of the group-level effect is to view data of all subjects as data from one “super-subject”, which contains \(N \times n\) observations [Monti, 2011].

**Random effect analysis** While the inferences from an FFX analysis are not invalid, such approach makes the assumptions that each subject makes the same contribution to the group-level observation and therefore ignores the specific variation that may pertain to each subject [Penny et al., 2007, Monti, 2011]. A second type of group analysis, namely the random effect (RFX) approach, addresses the limitation of FFX analysis by considering the magnitude of the effect in each subject to be a random variable [Monti, 2011]. As it is not possible to draw pure random effects inferences unless the true value of parameter estimates for each subject \((\beta)\) are known [Bianciardi et al., 2004, Monti, 2011], the group analysis approach described in this thesis used a so-called mixed effect model (MFX), which in essence combines a within-subject FFX analysis with a between-subject RFX analysis [Bianciardi et al., 2004, Beckmann and Jenkinson, 2003, Smith et al., 2005, Monti, 2011].

By introducing a between-subject error term, \(z_i\), which has zero mean and variance \(\text{var}[z_i] = \sigma^2_b\), the subject-level observation and group-level effect can be formulated as:

\[
y_{i,j} = m_g + z_i + e_{i,j}
\] (4.11)

\[
\hat{m}_g = \frac{1}{Nn} \sum_{i=1}^{N} \sum_{j=1}^{n} y_{i,j}
\] (4.12)

\[
\text{var}(\hat{m}_g) = \frac{\sigma^2_w}{Nn} + \frac{\sigma^2_b}{N}
\] (4.13)

**Summary statistics**

Similar to the matrix form of GLM at a single-subject level, the group-level GLM can be expressed as an “all-in-one” model [Beckmann and Jenkinson, 2003]:
\[ Y_G = X X_G \beta_G + \eta \] (4.14)

Here, \( Y_G \) is the data vector which contains the time series of all subjects (i.e., a vector that concatenates \( Y_i \) of each subject \( i \)), \( X \) is the single-subject design matrix, \( X_G \) is the group-level design matrix specifying how the individual subjects’ data are to be related (i.e., a vector of 1s indicating that each subject’s data should be averaged on the group-level), and \( \eta \) is the error term which characterizes both the within- and between-subject variances [Monti, 2011].

Despite of the simplicity of this “all-in-one” approach, in practice, computations based upon this approach can be intensive as it involves inverting huge matrices, especially for GLM analyses involving fMRI data [Monti, 2011, Poldrack et al., 2011]. For this reason, [Holmes and Friston, 1998] first proposed a computationally simpler hierarchical model of group analysis, which consists of two stages and is typically referred to as the summary statistics approach [Monti, 2011]. Specifically, this approach first performs the GLM analysis on a single-subject level. The subject-specific parameter estimates are then carried forward to the group-level analysis where the across-subject effect is estimated. Such single-subject estimates could be the \( \hat{\beta} \)'s, or a contrast of interest, \( c \hat{\beta} \), formulated with a contrast vector \( c \) and the parameter estimates \( \hat{\beta} \) [Beckmann and Jenkinson, 2003, Penny et al., 2007, Monti, 2011].

### 4.2.2 Threshold-free cluster enhancement

For GLMs that investigated the relationship between the EEG discriminating component and behavioral or pupillary measures, a threshold-free cluster enhancement (TFCE) [Smith and Nichols, 2009] was applied to determine the significance level of the parameter estimates. Here, the input to the TFCE algorithm was the time series of parameter estimates (or the t-statistics of the estimates) at training windows of interest. The use of TFCE on the time series of correlation values ensured detection of both diffuse, low-amplitude correlations (i.e. weak but long-lasting) and sharp, local correlations (i.e. strong but short-lived), as demonstrated in Figure 4.2.

Specifically, each input’s TFCE score is given by the sum of the scores of all “supporting sections” underneath it. As the height \( h \) is incrementally raised from zero up to the height \( h_p \) of a given point
45

Figure 4.2: Threshold-Free Cluster Enhancement. Illustration of the TFCE approach. Reprinted by permission from Elsevier: Elsevier, NeuroImage, [Smith and Nichols, 2009], Copyright © 2008 Elsevier Inc.

$p$ (height here refers to the amplitude of the parameter estimate or t-statistics of the parameter estimate), the estimate is thresholded at $h$, and the single contiguous cluster containing $p$ is used to define the score for that height $h$. This score is simply the height $h$ (raised to some power $H$) multiplied by the cluster extent $e$ (raised to some power $E$). Precisely, the TFCE output at time point $p$ is:

$$TFCE(p) = \int_{h=h_0}^{h_p} e(h)^E h^H dh$$

(4.15)

Here, $h_0$ will typically be zero, with $E$ and $H$ set to 0.5 and 2 respectively [Smith and Nichols, 2009, Pernet et al., 2015]. In practice this integral is estimated as a sum, using a finite $dh$ [Smith and Nichols, 2009].

For each pair of dependent and independent variables tested, a null distribution of TFCE scores was first constructed by permuting the vector of single-trial measurements multiple times (1000 times in the simultaneous pupil-EEG experiment, and 5000 times in the simultaneous pupil-EEG-fMRI experiment), and computing the TFCE scores for the parameter estimates or the t-statistics of the parameter estimates in each permutation. Parameter estimates were used to compute corresponding TFCE scores in the simultaneous pupil-EEG experiment, and t-statistics of the parameter estimates were used to compute their TFCE scores in the simultaneous pupil-EEG-fMRI experiment (the t-statistics of the parameter estimates were used for computation speed purposes, as
it called for larger \( dh \) and required fewer steps to integrate over the “supporting sections”). The significance level was determined by thresholding to the TFCE score corresponding to \( p < 0.05 \).

### 4.3 Simultaneous pupil-EEG experiment

In the following section, we discuss the analysis approaches specific to the simultaneous pupil-EEG experiment.

#### 4.3.1 Single modality analysis

**Pupillometry data analysis**

Two pupil diameter measurements were extracted, namely the prestimulus PDB and the poststimulus PR. The PDB was defined as pupil diameter at stimulus onset time. The PR was defined as the maximum percentage deviation from baseline pupil diameter within each epoch. These two measures were used to index the tonic and phasic level of arousal, respectively.

**EEG data analysis**

Traditional ERP and single trial EEG analysis were performed as described in Section 4.1.

**Prestimulus alpha oscillations analysis**

Apart from PDB, the magnitude of EEG alpha oscillations was also investigated as another prestimulus measurement. To estimate the magnitude of prestimulus alpha oscillations for each oddball trial, an ICA was first performed on the EEG data. A single “alpha component” was selected based on two criteria: 1) the component with the highest ratio of mean power in the 8 to 12 Hz alpha band relative to mean power in adjacent bands (5 to 8 Hz theta band and 12 to 20 Hz beta band), which 2) also had a posterior scalp topography. The alpha activity from this component was estimated using a band-pass filter (with a bandwidth of 4 Hz) centered on the subject-specific alpha frequency, which was determined based on the peak in the power spectral density of the unfiltered EEG. A Hilbert transform [Duoandikoetxea, 2001] was used to construct the envelope of alpha oscillations across time. Lastly, the magnitude of prestimulus alpha oscillations for each trial was obtained by averaging this envelope in the –500 to 0 ms time range prior to the stimulus.
4.3.2 Dual modality analysis

GLM and statistical analyses

Specifically, for each time window, \( \tau \), between 0 ms and 1000 ms poststimulus onset, a general linear model was used to fit the de-meaned output of the logistic regression based classifier, \( \tilde{y}_i = y_i - y_{\text{mean}} \), for each trial, \( i \) (see Figure 4.1). The following four measurements of interest were used as predictor variables: 1) RT, 2) magnitude of prestimulus alpha oscillations (pre-EEG\( \alpha \)), 3) PDB, and 4) PR. Note that for convenience we dropped the \( \tau \) from our notation since a given \( \tilde{y}_i \) is always implicitly linked to a given time window \( \tau \) (i.e. the expression \( \tilde{y}_i = y_i - y_{\text{mean}} \) and \( \tilde{y}_i(\tau) = y_i(\tau) - y_{\text{mean}}(\tau) \) are equivalent). All measurements were z-scored within each subject before subsequent analyses.

As previously discussed in Section 4.2, we performed a hierarchical, i.e. single-subject carried through to group-level GLM analyses between each of the four measurements and \( \tilde{y} \)'s spanning the entire trial. Each GLM was designed to examine both linear and quadratic relationships between measurements of interest, by including both linear and squared terms as regressors, and orthogonalizing the quadratic regressor to the linear regressor. Specifically, for each GLM, one of the four measurements was fit to \( \tilde{y} \). By repeating this fit for windows at different poststimulus times, a vector of coefficient estimates (\( \beta \)) was obtained. \( \beta \) therefore showed a progression of linear and quadratic estimates over time. A large \( \beta \) for the linear term is indicative of a strong linear relationship and a large \( \beta \) for the quadratic term indicates a strong quadratic relationship. Furthermore, the sign of \( \beta \) in the quadratic term indicates the direction of concavity/convexity: positive quadratic \( \beta \) indicates that the relationship is U-shaped (convex), while negative quadratic \( \beta \) indicates an inverted U-shape (concave). The significance level of the parameter estimates were assessed with the TFCE approach described in Section 4.2.2.

In order to tease apart correlates that were observable in RT from latent variability in the poststimulus EEG component, the correlation analyses was also repeated after linearly regressing out RT from the discriminating component variability \( \tilde{y} \).

Our primary analyses focused on linear and quadratic relationships between the EEG discriminating component variability of oddball trials and RT, pre-EEG\( \alpha \), PDB and PR. In addition, pairwise linear and nonlinear relationships were also investigated between these four attention-related measures through the previously described GLM methods. For pairwise GLM analyses, the
results and their interpretation depend on the form of the GLM, e.g. choosing which measurement is the predictor variable and which is the response variable. In particular, 1) we always fit pupil and EEG measures to RT since RT is a measure of task performance; 2) we always fit pupil measures to EEG measures since the latter better characterizes task performance than the former, and 3) we always fit prestimulus pupil measures to poststimulus pupil measures since the latter is an evoked response. In this way, we were able to study the relationships between behavioral, neural and pupillary measures both before and after the stimulus.

4.4 Simultaneous pupil-EEG-fMRI experiment

In the following section, we discuss the analysis approaches specific to the simultaneous pupil-EEG-fMRI experiment. The addition of fMRI acquired data in this experiment expanded the possibilities of cross modality analyses. Specifically, in addition to the single and dual modality analyses previously described in the simultaneous pupil-EEG experiment, we now have the opportunity to 1) explore the pairwise relationship between measures of interest with combined EEG-fMRI and pupil-fMRI dual modality analyses, and 2) examine the spatiotemporal interactions between systems of interest with combined pupil-EEG-fMRI triple modality analyses. The heavy emphasis of fMRI related analyses therefore demands a more in-depth discussion of BOLD signal centric GLM analyses, so as to facilitate discussions of results in the ensuing chapters.

Consequently, we first provide a brief overview of the key stages in an fMRI analysis in Section 4.4.1, followed by a discussion of our unique approach in constructing BOLD signal centric GLM analyses with STV in Section 4.4.2, which applies to all following dual and triple modality analyses involving the BOLD signal.

The rest of this section will describe the specific details in single or cross modality analyses employed in this experiment.

4.4.1 Traditional fMRI analysis

The BOLD response

The most common method of fMRI takes advantage of the fact that when neurons in the brain become active, the amount of blood flowing through that area is increased. This increase in blood
flow that follows a brief period of neuronal activity is called the hemodynamic response (HR). This phenomenon has been known for more than 100 years, though the mechanisms that cause it remain only partly understood. What is particularly interesting is that the amount of blood that is sent to the area is more than is needed to replenish the oxygen that is used by the activity of the cells. Thus, the neuronal activity related increase in blood flow leads to a relative surplus in local blood oxygen. The signal measured in fMRI depends on this change in oxygenation and is referred to as the blood oxygenation level dependent, or BOLD, signal [Poldrack et al., 2011].

Extracting information entailed in the BOLD response

As described above, in essence, the BOLD signal reflects activity changes in the brain. The goal of a task-related BOLD signal analysis can therefore be broken down into two parts: 1) to examine what factors or experimental manipulation contributed to changes in the BOLD response; and 2) if so, where did it take place in the brain. In other words, the motivation behind an event-related fMRI analysis is to identify regionally specific effects with the acquired neuroimaging data.

[Penny et al., 2007] presented a suite of methods and tools to perform such analyses, which they called “statistical parametric mapping”. This approach is used to identify regionally specific effects in neuroimaging data and is a prevalent approach to characterizing functional anatomy, specialization and disease-related changes. Statistical parametric mapping is also a mass univariate approach (i.e., voxel-based approach) - it analyzes each and every voxel, and uses topological inference to make some comment about regionally specific responses to experimental factors [Penny et al., 2007].

The two pillars in a statistical parametric mapping approach are the general linear model and random field theory (RFT). GLM provides the bridge between theoretical contributing factors and observed data, by inverting generative models of the data to partition observed responses into components of interest, confounds and noise. Inferences are then pursued using statistics that compare interesting effects and the error. In order to correct for multiple comparison issues that followed after the examination of numerous voxels across the whole brain, RFT is called upon to provide a method for adjusting p-values for the search volume and plays the same role for continuous data (i.e., images) as the Bonferroni correction does for a number of discontinuous or discrete statistical tests [Penny et al., 2007].
To put it concisely, the two-fold goal of an fMRI analysis can be achieved by generating a hypothetical model of brain activity and using multiple linear regression to search for voxels correlated with the predicted response [Grinband et al., 2008].

The explanatory variable in such regression analysis is the design matrix that captures the hypothetical model of neuronal activity. The response variable, on the other hand, is the measured BOLD response. Much like any other statistical modeling, without careful model specification, interpretable inferences will become far-fetched. Moreover, in the case of fMRI analysis, accurate translation from the model to the expected BOLD response are also critical for subsequent parameter estimation and inference.

In a typical task-related fMRI analysis, the two key elements of a design matrix are the stimulus functions which encode the occurrence of particular events, and the expected shape of the BOLD response elicited by these events. The stimulus function models the hypothetical evoked neuronal responses (with boxcar functions of epoch-related responses or spike-(delta)-functions at the onset of specific events or trials), which are then convolved with a hemodynamic response function (HRF) to give the expected hemodynamic response [Penny et al., 2007]. This predicted response constitutes the design matrix, which is then compared with the measured BOLD response at voxels across the whole brain, in search of the particular voxels whose measured responses correlate with the expected one, allowing inferences to be made on where neuronal responses are expressed.

In other words, the signal in fMRI time-series corresponds to neuronally mediated hemodynamic changes that can be modelled as a convolution of some underlying neuronal process, responding to changes in experimental factors, by an HRF [Penny et al., 2007].

### 4.4.2 Single trial variability informed fMRI analysis

In the previous section, we provided a brief overview of the motivation behind using fMRI and the acquired BOLD signal. We then discussed how a hypothetical model encoding underlying neuronal activity could be 1) constructed and transformed to express the expected BOLD response (via convolution and GLM), and 2) how the expected BOLD response could be correlated with the measured BOLD signal, in searching of voxels where the neuronal responses are present (via GLM and RFT). In this section, we will focus on our innovative approach of building the hypothetical model - namely, in constructing the design matrix of a GLM.
Two types of regressors

The first step of a classical GLM analysis is the model specification. A well-defined model is crucial for all subsequent steps, including parameter estimation and inference. What to put inside the model, however, depends on the question one intends to ask.

In the simultaneous pupil-EEG-fMRI experiment, our interest lies in the timing and location of the neural activity following a target detection task. More specifically, we wish to examine if the neuronal responses fluctuate even with identical stimulus input, and if so, to what extent do they vary. Our hypothesis for BOLD signal centric analysis can therefore be formulated into two parts. First, we hypothesize that the external stimulus input will elicit certain neural responses that are consistent across trials - i.e., certain brain regions will always be activated whenever the stimulus took place. This first type of neural activity is in essence void of trial-to-trial variability. Second, we hypothesize that the endogenous fluctuations can be reflected in the unique variabilities of neural responses of each trial. In other words, specific brain regions will be sensitive to the variability from trial-to-trial.

Consequently, the following model specification in the GLM analysis reflects the above described hypothesis. The first type of regressors we construct correspond to the stimulus, and the second type of regressors represent the trial-to-trial variability that could encode important information of the endogenous fluctuations.

Operationally, model specification corresponds to setting up the regressors, or stimulus function, which models the hypothetical neuronal responses (we will omit the convolution step as it has been discussed in the previous section). The three key elements of a regressor are the onset, duration, and height of the events or factors that are likely to contribute to the neural activity and subsequent BOLD signal measurements.

For the first type of regressor which corresponds to the stimulus, we model it without any modulation. The onset of the regressor is the onset time of the stimulus throughout the experiment, and the duration of the regressor is fixed to the duration of the stimulus. The height of the regressor is set to 1, indicating the presence of a particular stimulus type [Penny et al., 2007].

For the second type of regressor which represents the trial-to-trial variability, we use an approach called parametric modulation. The onset of the regressor is set to the time of interest, and the duration of the regressor is fixed to 100 ms. The height of the regressor is now parametrically
modulated, i.e., weighted with the STV from measures of interest, and is therefore specific from trial-to-trial.

**Inference formulation**

In terms of making inferences, if the measured BOLD signal of certain voxel correlates significantly with the expected BOLD response formulated from the stimulus regressor, the neural activity of that voxel should depend on the stimulus. If, however, the measured BOLD signal of certain voxel correlates significantly with the expected BOLD response formulated from the STV regressor, the neural activity of that voxel should be sensitive to the trial-to-trial variability.

It is worth noting that the type and subsequent interpretation of trial-to-trial variability depends on the measures of interest from which the variability was derived. For instance, trial-to-trial variability in the EEG discriminating component at an early window could be reflective of the variability in sensory input processing; whereas trial-to-trial variability in the PDB could represent the fluctuations of tonic activity of the arousal system.

**GLM with pre-whitening**

Lastly, for GLM analysis involving the BOLD response, one aspect worth mentioning is the necessity of applying pre-whitening on the data. Recall that the optimal parameter estimates as per the OLS algorithm can be deduced from $Y = X\beta + \epsilon$, where $Y$ is the dependent variable vector, $X$ is the independent variable matrix, $\beta$ is the parameter vector, and $\epsilon$ is the error vector. The parameter estimates, $\hat{\beta}$, have the following characteristics:

$$\hat{\beta} = (X^T X)^{-1} X^T Y, \quad \text{var}(\hat{\beta}) = \sigma^2 (X^T X)^{-1}$$

According to the Gauss–Markov theorem, the OLS estimates will correspond to the best linear unbiased estimator (BLUE) of the population parameters, in the class of unbiased estimators, if certain assumptions relating to the properties of the error term and the parameters hold true [Monti, 2011]. With respect to the error term, the assumption for the OLS estimates to be optimal is that the errors are independently and identically distributed (i.i.d.), i.e., $\epsilon \sim N(0, \sigma^2 I)$, where $I$ is an identity matrix corresponding to the size of the error vector [Monti, 2011]. The BOLD signal,
however, may exhibit correlations between residuals at successive time-points. Such temporal autocorrelations can violate the i.i.d. assumption described above [Monti, 2011].

When data are temporarily autocorrelated, pre-whitening removes this correlation from the GLM prior to estimation [Poldrack et al., 2011]. In general, the pre-whitening process is carried out in two steps. In the first step, the GLM is fit ignoring temporal autocorrelation to obtain the model residuals, which is the original data with all modeled variability removed. The residuals are then used to estimate the autocorrelation structure, and then model estimation is carried out after pre-whitening both the data and the design matrix [Poldrack et al., 2011].

The best solution for the parameter estimates can then be obtained by pre-multiplying $Y$ and $X$ by $K$, where $KV K^T = I$:

$$KY = KX \beta + K\epsilon, \quad K\epsilon \sim N(0, \sigma^2 I)$$  \hspace{1cm} (4.17)

Finally, as discussed in Section 4.2, GLM analyses were carried out in a hierarchical manner. While the first-level analyses involved different predictor variables for different cross modality analyses, the second-level analysis remained the same across analyses, and is described here: the second-level analysis was carried out with an FFX model, as the aim was to average contrasts estimates over runs within each subject. The RFX variance is forced to zero in FMRIB’s Local Analysis of Mixed Effects (FLAME) [Beckmann and Jenkinson, 2003, Woolrich et al., 2004, Woolrich, 2008]. The group-level analysis was carried out using a mixed effects model, using FLAME stage 1 [Beckmann and Jenkinson, 2003, Woolrich et al., 2004, Woolrich, 2008]. In order to assess the significance level of the parameter estimates, $z$ statistic images were thresholded using clusters determined by $z > 3.1$ for traditional fMRI analysis, and $z > 2.3$ for dual and triple modality analyses, along with a (corrected) cluster significance threshold of $p = 0.05$ [Worsley, 2001], with Gaussian Random Field (GRF) theory.

4.4.3 Single modality analysis

Pupillometry data analysis

Similar to that in the simultaneous pupil-EEG experiment, we examined two pupil diameter measurements - the prestimulus PDB and poststimulus PR. The PDB was defined as average pupil
diameter from 500 ms prestimulus to stimulus onset time. The PR was defined as the maximum percentage deviation from stimulus onset time to 2000 ms poststimulus.

**EEG data analysis**

Traditional ERP and single trial EEG analysis were performed, as described previously in Section 4.1.

**fMRI data analysis**

Traditional fMRI analyses were carried out using FSL [FMRIB, 2018]. The time-series statistical analysis was carried out using FILM with local autocorrelation correction, via the pre-whitening approach [Woolrich et al., 2001]. This conventional fMRI analysis was designed to identify stimulus-specific brain regions. Specifically, locking at the time of stimulus, we constructed three boxcar regressors: 1) two unmodulated regressors corresponding to the time of standard and oddball stimulus, respectively. The regressors have the duration of the stimulus (200 ms), and the height of 1; 2) a modulated regressor corresponding to the time of oddball stimulus, with corresponding behavioral response time of each trial as the duration for each regressor event, and a height of 1. Movement estimated in the pre-processing step were included as nuisance regressors. Temporal derivatives of all regressors were included in the model, and we used canonical double gamma HRF for convolution. RT regressor was orthogonalized with respect to the unmodulated oddball regressor - so that the latter takes full credit for variability related to the task, while the estimates for the former represents unique variability related to response time. In the traditional fMRI analysis, our primary interest lies in the differences in brain activations explained by standard and oddball stimuli, respectively (contrast of $c = [-1 1 0]$, with regressor vector of [standard, oddball, RT]).

**4.4.4 Dual modality analysis**

**GLM analysis with concurrent pupil-EEG data**

Similar to the approach described in Section 4.3, for each time window, we used a GLM to fit the de-meaned EEG discriminating component of each trial, $\tilde{y}_i$, to the measure of interest of each corresponding trial. This is carried out for all measures of interest (i.e., RT, PDB, and PR). We
also linearly regressed out RT from $\tilde{y}$, and used the residual $\tilde{y}$ to correlate with pupillary features of interest.

In addition to investigating the relationship between EEG discriminating component and measures of interest, we also examined the extent to which measures of interest covary with each other. Once again, 1) we always fit pupil measures to RT since RT is a measure of task performance and 2) we always fit prestimulus pupil measures to poststimulus pupil measures since the latter is an evoked response.

GLM analysis with concurrent EEG-fMRI data

Dual-modality EEG-fMRI analysis was carried out using FSL [FMRIB, 2018]. The time-series statistical analysis was carried out using FILM with local autocorrelation correction, via the pre-whitening approach [Woolrich et al., 2001]. This analysis was designed to identify brain regions sensitive to the trial-to-trial variability of temporally specific neural processes, and bore a certain resemblance to the conventional GLM we described in Section 4.4.3.

The difference in the two GLMs lies in the parametrically modulated terms, as discussed in Section 4.4.2. Specifically, in addition to the three major regressors we described in the traditional GLM, another two parametrically modulated regressors were introduced in the EEG-fMRI GLM. Recall that for each time window, a de-meaned EEG discriminating component for all trials, $\tilde{y}_i(\tau)$, were obtained (with $\tau$ representing the window and $i$ representing the trial). For oddball or standard trials, this EEG component therefore was representative of the classifier’s confidence in discriminating neural responses of oddball from standard stimulus at different poststimulus time, or vice versa.

Consequently, we constructed two EEG component informed regressors corresponding to either the oddball or standard trials. The oddball EEG STV regressor corresponded to the STV in EEG discriminating component of the oddball trials, whereas the standard EEG-STV regressor corresponded to that of the standard trials. The two regressors were both locked to the window of interest ($\tau$), with a height of $\tilde{y}_i(\tau)$ ($i$ here represents the oddball or standard trials, depending on the regressor). Note that as we were mostly interested in neural processes associated with attention reorienting, all following analyses will focus only on results related with the oddball trials, where subjects attended to the task-relevant stimulus.
The EEG-fMRI GLM therefore consisted of five regressors of interest: two unmodulated stimulus-specific regressors, one duration-modulated RT regressor, and two amplitude-modulated EEG-STV informed regressors. This type of GLM was constructed and analyzed independently at all windows with substantial classifier performance, i.e. from 225 ms to 625 ms poststimulus, ensuring sufficient degrees of freedom for the regression analysis. Figure 4.3 illustrates the details.

Additionally, movement estimated in the pre-processing step were included as nuisance regressors. Temporal derivatives of all regressors were included in the model, and we used canonical double gamma HRF for convolution. RT regressor was orthogonalized with respect to the unmodulated oddball regressor, EEG-STV regressors were orthogonalized with respect to the corresponding stimulus regressors, with oddball EEG-STV regressor also orthogonalized to RT regressor. As our primary interest lies in identifying the spatial correlates of trial-to-trial variability in the oddball EEG discriminating component, we will focus our discussion on the contrast including only the oddball EEG-STV regressor term ($c = [0 \ 0 \ 0 \ 1 \ 0]$, with regressor vector of [standard, oddball, standard EEG-STV, oddball EEG-STV, RT]).

**GLM analysis with concurrent pupil-fMRI data**

Dual-modality pupil-fMRI analysis was carried out using FSL [FMRIB, 2018]. The time-series statistical analysis was carried out using FILM with local autocorrelation correction, via the pre-whitening approach [Woolrich et al., 2001]. This analysis was designed to identify brain regions sensitive to the trial-to-trial variability of prestimulus PDB or poststimulus PR, and bore a certain resemblance to the EEG-fMRI GLM we described in Section 4.4.2.

We constructed four pupil STV informed regressors corresponding to either the stimulus type or the pupillary measures of interest. Specifically, locking to the time of oddball stimulus, the oddball PDB STV regressor corresponded to the STV in prestimulus PDB of the oddball trials, and the oddball PR STV regressor corresponded to the STV in poststimulus PR of the oddball trials. Similarly, locking to the time of standard stimulus, we created the standard PDB STV regressor as well as the standard PR STV regressor.

The pupil-fMRI GLM therefore consisted of six regressors of interest: two unmodulated stimulus-specific regressors, and four amplitude-modulated pupil-STV informed regressors. Additionally, movement estimated in the pre-processing step were included as nuisance regressors. Temporal
Figure 4.3: EEG STV informed fMRI analysis. Illustration of EEG STV informed fMRI analysis. (I) Sequence of stimuli. (II) Application of sliding window technique as described in Section 4.1. EEG signal within the sliding window for each trial, $x_i, i = 1, ..., 5$, is highlighted in the shaded regions. (III) The EEG discriminating component, $y_i$, is computed with $x_i$ from the specific window via logistic regression. GLM is then constructed with two conventional regressors (unmodulated), one RT regressor (duration-modulated by RT of each oddball trial), and two EEG STV regressors (amplitude-modulated by their $y$ value).
CHAPTER 4. DATA ANALYSIS

derivatives of all regressors were included in the model, and we used canonical double gamma HRF for convolution. As our primary interest lies in identifying the spatial correlates of trial-to-trial variability in the oddball PDB and PR, we will focus our discussion on the contrast including only the oddball pupil-STV regressor term \( (c = [0 0 0 0 1 0]) \), as well as \( c = [0 0 0 0 0 1] \), with regressor vector of [standard, oddball, standard PDB-STV, standard PR-STV, oddball PDB-STV, oddball PR-STV]).

4.4.5 Triple modality analysis

GLM analysis with concurrent pupil-EEG-fMRI data

Triple modality pupil-EEG-fMRI analysis was carried out using FSL [FMRIB, 2018]. The time-series statistical analysis was carried out using FILM with local autocorrelation correction, via the pre-whitening approach [Woolrich et al., 2001]. This analysis was designed to identify brain regions sensitive to the trial-to-trial variability of the interaction between pupillary features and EEG component of interest. Considering the ongoing and preliminary nature of our analyses, here we describe solely the GLM construction with respect to the interaction between PDB and EEG discriminating component at a late window (525 ms). Such interaction analysis was determined based on the pupil-EEG analysis results, where we observed a significant correlation between PDB and this late window EEG variability.

In addition to the pupil and EEG STV informed regressors described in previous chapters, we constructed two additional regressors to capture the interaction between pupil-linked arousal and neural activity at various poststimulus times. Specifically, locking to the time of the sliding window, the height of the standard and oddball PDB x EEG interaction STV regressors corresponded to the product of STV in prestimulus PDB and STV in EEG component of standard and oddball trials, respectively.

The pupil-EEG-fMRI GLM therefore consisted of nine regressors of interest: two unmodulated stimulus regressor, one duration modulated behavioral response regressor, two amplitude-modulated PDB STV informed regressors (standard and oddball PDB STV), two amplitude-modulated EEG STV informed regressors (standard and oddball EEG component STV), and two amplitude-modulated PDB x EEG interaction STV informed regressors (standard and oddball PDB x EEG component interaction STV). Additionally, movement estimated in the pre-processing step
were included as nuisance regressors. Temporal derivatives of all regressors were included in the model, and we used canonical double gamma HRF for convolution. As our primary interest lies in identifying the spatial correlates of the interaction between trial-to-trial variability in the oddball PDB and EEG component, we will focus our discussion on the contrast including only the oddball PDB x EEG-STV regressor term \( \mathbf{c} = [0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 1 \ 0] \), with regressor vector of [standard, oddball, standard PDB-STV, oddball PDB-STV, standard EEG-STV, oddball EEG-STV, standard PDB x EEG-STV, oddball PDB x EEG-STV, RT]).
Chapter 5

Simultaneous pupil-EEG experiment

This chapter discusses our early stage findings in connecting pupil-linked arousal to neural processes engaged in attention reorienting, with simultaneous pupil-EEG recording. The contents of this chapter are organized into three parts: we start with an overview of this cross modality analysis, followed by the major results and a brief discussion of the key findings. The ensuing chapters follow the same structure - specifically, we aim to first deliver the pieces of information one could glean from each dual or triple modality analyses, before the ultimate assembly takes place in the final discussion chapter.

5.1 Introduction

As introduced in Section 1.3, pupillary measures have been shown to correlate strongly with a variety of measurements of cortical state and behavioural arousal, which is controlled by neuro-modulatory systems such as the LC-NE system [Eldar et al., 2013, Reimer et al., 2014, Vinck et al., 2015, McGinley et al., 2015a, McGinley et al., 2015b, Engel et al., 2016, van Kempen et al., 2019]. There is also evidence that evoked EEG responses, such as the P300, might have LC-NE activity as their basis [Astaiev et al., 2003, Clayton et al., 2004, Strange and Dolan, 2007, Corbetta et al., 2008]. Since it is not feasible to record electrophysiological data directly from the LC in humans due to the nucleus’ location in the brainstem, an open question has been whether pupillary measures and EEG variability can be linked in a meaningful way to shed light on the nature of the LC-NE’s role in modulating attention and arousal.
In this study, we used a data-driven approach to learn task-relevant projections of the EEG for an auditory oddball task. We temporally localized the projections across the entire trial and subsequently correlated the variability of the EEG along these projections with prestimulus PDB and poststimulus PR pupillary measures, providing further insight regarding the link between prestimulus and poststimulus cortical and subcortical processes underlying target detection.

5.2 Results

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.1 and 4.3.

5.2.1 Behavioral performance

All fourteen subjects performed the task at high accuracy with 99.3% ± 0.2% of oddballs correctly detected. Average reaction time (RT) was 398.4 ± 23.9 ms.

5.2.2 Trial-averaged analysis

We first analyzed trial-averaged ERPs and PRs for both oddball and standard trials, to quantify the magnitude of the differences in the average evoked activity. Figure 5.1 shows the resulting ERPs. The N100-P200 complex can be seen at fronto-central electrode sites (Fz, Cz), followed by the N200 component, which was larger for oddballs than standards on posterior scalp sites (shown on Pz). In contrast, anterior N200 was larger for standards than oddballs, as seen from frontal and central electrodes (Fz, Cz). This is consistent with results from many oddball paradigms [Folstein and Van Petten, 2008]. Lastly, the P300 component was evident and most prominent on the parietal (Pz) electrode, peaking at approximately 350 ms poststimulus.

Both oddball and standard stimuli evoked pupil diameter increases after the stimulus (Figure 5.2). An early dilation peak was seen at 500 to 600 ms poststimulus for both standard and oddball trials. This is consistent with the results of [Steinhauer and Hakerem, 1992], who described pupil dilations caused by inhibition of parasympathetic pathways. The primary dilation, i.e. the maximum pupil dilation evoked by oddball stimuli, was reached at approximately 1350 ms. Consistent with well-established pupillometry findings, the pupil dilation following oddball stimuli was
Figure 5.1: Grand mean ERPs at electrodes Fz, Cz and Pz. Shown are grand average stimulus-locked curves from 200 ms prestimulus to 1000 ms poststimulus for oddball (pink) and standard (green) stimuli, with shaded bands indicating standard error across subjects ($N = 14$).
Figure 5.2: Evoked pupillary response. Grand average stimulus-locked curves from 200 ms prestimulus to 2000 ms poststimulus for oddball (pink) and standard (green) stimuli, with shaded bands indicating standard error across subjects ($N = 14$). Traces have units of percentage change from the mean.
larger than the dilation following standards [Steinhauer and Hakerem, 1992].

5.2.3 Single-trial EEG analysis

We next analyzed the single-trial EEG in order to correlate fluctuations in pupil diameter with the temporally localized task-relevant EEG. Group mean single-trial EEG discriminator performance (shown in panel I of Figure 5.3) was significant for all consecutive windows between 75 ms and 850 ms poststimulus ($p < 0.01$ for AUC $> 0.62$, computed via permutation test). The subject-averaged performance reached its peak of AUC = 0.91 at 350 ms. Corresponding forward models for a subset of windows with significant discrimination are shown in the top row of panel III in Figure 5.3. Discriminating activity around 200 ms was strongest at central sites and more negative for oddballs compared to standards. This spatial distribution and peak latency was characteristic of the N200 component. In addition, strong positive activity at parietal sites lasted from 350 ms to 500 ms and was consistent with the P300 ERP component.

5.2.4 GLM analysis

We next conducted our correlation analysis between poststimulus EEG discriminant component variability for oddball trials and behavioral and pupil diameter measurements. First we considered correlations between poststimulus EEG component and RT. Panel II of Figure 5.3 indicates significant negative correlation between these two measurements for all but two consecutive windows from 150 ms to 575 ms. Previous work has shown that much of the LC activity and the late phases of the P300 response are locked to reaction time [Gerson et al., 2005, Aston-Jones and Cohen, 2005]. In order to capture variability that is unique to the EEG latent states and not attributable to behavioral measures, such as RT, we regressed out RT from poststimulus EEG component. The bottom row in panel III of Figure 5.3 shows the resulting forward models after the linear contribution of RT variability was removed. The major difference between these scalp topologies and the ones prior to decorrelating with respect to RT was seen during the P300 time window of 350 ms to 500 ms.

Panel IV in Figure 5.3 shows the results of fitting linear and quadratic models of PDB to residual poststimulus EEG component (i.e., EEG component after regressing out RT from the component). We found only significant negative linear relationships between PDB and poststimulus
Figure 5.3: Correlation between RT, baseline pupil diameter (PDB) and EEG component variability. Shown are group-level results for EEG windows spanning the trial, with shaded regions denoting $p < 0.05$ (corrected) significance for linear (dark grey) or quadratic (light grey) relationships. (I) EEG classifier performance as defined by area under the ROC curve (dark purple trace). $p = 0.01$ (AUC = 0.62) threshold is indicated with a light purple dotted line. (II) Linear (dark grey) and quadratic (light grey) GLM fit coefficient estimates, $\beta$, between RT and poststimulus EEG component (classifier output $y$) as a function of window time. (III) Subset of scalp topographies generated using $y$ (top row) and residual $y$ (after regressing out RT, bottom row). (IV) Linear (dark grey) and quadratic (light grey) GLM fit coefficient estimates between PDB and poststimulus EEG component.
Figure 5.4: Pairwise correlations between RT, baseline pupil diameter, evoked pupillary response and magnitude of prestimulus alpha. Shown are linear (dark grey) and quadratic (light grey) GLM fit coefficient estimates ($\beta$) between the four measurements: RT, PDB, PR and pre-EEG$\alpha$. For each pairwise GLM fit, measurement label on the top is the response variable, while measurement on the bottom is the predictor variable. Standard error bars are across subjects ($N = 14$). Significant correlations ($p < 0.01$) are denoted by double asterisks, with dashed line at zero correlation.
EEG component, while the timing of this significant correlation aligned with the latencies of the N200 and P300 ERPs.

We investigated several additional correlations in our analysis. First we looked at whether prestimulus alpha (pre-EEG$_\alpha$) covaried with poststimulus EEG component, and no significant relationships between this measurement and poststimulus EEG component were found. We also investigated the relationship between PR and poststimulus EEG component for both are poststimulus evoked response; neither linear nor quadratic relationships between these two measurements reached significant level ($p < 0.05$) after multiple comparison correction. Figure 5.4 also shows pairwise correlations between the four measurements. Notably, PR is negatively correlated with pre-EEG$_\alpha$. We also observed that large pupillary responses were linked to longer RTs.

5.3 Summary

In this simultaneous pupil-EEG experiment, we examined the relationship between internal arousal states and neural processes involved in attention reorienting. We used pupillometry features to index the activities of the arousal system, and found that PDB correlates with early window (175 to 200 ms) and middle window (350 to 400 ms) EEG component variability, suggesting a relationship between baseline (tonic) LC-NE activity and evoked EEG. Surprisingly we found no correlation between EEG variability and PR, which is often associated with evoked (phasic) LC activity. After regressing out RT, we found that the correlation between EEG variability and PDB remains, suggesting that such correlation is not explainable by RT variability. We also investigated the relationship between these pupil measures and prestimulus EEG alpha activity, which has been reported as a marker of attentional state, and found a negative correlation with PR. Taken together, our results demonstrate significant correlations between prestimulus and poststimulus neural and pupillary measures, provide further evidence for tight coupling between attentional state and evoked neural activity, and also the role of cortical and subcortical networks underlying the process of target detection.
Chapter 6

Simultaneous pupil-EEG-fMRI experiment: single modality analysis

6.1 Introduction

Starting from this chapter, we present the main focus of this thesis - findings from the simultaneous pupil-EEG-fMRI experiment. The following chapters are organized with respect to the number of modalities involved. Chapter 6 starts with analyses utilizing single modalities. Chapter 7, 8, and 9 commence the cross modality analyses with pairwise (dual) modality analysis. As discussed previously, in the context of this thesis, pairwise modality analysis investigates the relationship between two modalities of data, typically by using information from one modality to inform another. In Chapter 10, we present results with triple modality analysis, which incorporates data across all three modalities to make inferences.

In this chapter, we begin by first demonstrating the impact of artifact removal in EEG data, as a justification for the necessity of removing confounding artifacts from EEG, as described in depth in previous chapters (see Section 3.1.2). The remaining of the chapter summarizes the results from single modality analyses.
6.2 Results

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.2 and 4.4.

6.2.1 Impact of artifact removal in EEG data

Here we present the stimulus-locked ERPs before and after artifact removal at three midline recording sites: Fz, Cz and Pz. Figure 6.1 demonstrates the differences in ERPs before and after artifact removal at Fz. As the frontal electrodes are more strongly affected by blink artifacts, it is unsurprising that the ERP before artifact removal exhibited a larger downward spike and also a larger standard error in the vicinity of 500 ms.

ERPs at electrode Cz, on the contrary, were less susceptible to blinks (Figure 6.2), although the overall amplitude after artifact removal did diminish slightly. Such effect after blink artifact removal is also present for the ERPs at electrode Pz, as shown in Figure 6.3.

6.2.2 Behavioral performance

All nineteen subjects performed the task at high accuracy with 99.4\% ± 0.1\% of oddballs correctly detected (with an average miss rate of 1.4\%). Average RT was 414.7 ± 69 ms.

6.2.3 Trial-averaged pupil analysis

Figure 6.4 demonstrates the evoked pupil response for both standard and oddball stimuli. Note that the baseline pupil diameter is not removed, as we are interested in investigating the trial-to-trial variability of this measure. With respect to the poststimulus pupillary response, the pupil dilation evoked by oddball stimuli reached its peak around 1500 ms, consistent with results from the simultaneous pupil-EEG experiment (see Figure 5.2).

6.2.4 Trial-averaged EEG analysis

Figures 6.1, 6.2, and 6.3 show the trial-averaged ERPs for oddball and standard trials. The N100-P200 complex are present at fronto-central electrode sites (Fz, Cz), followed by the prominent
Figure 6.1: ERP at electrode Fz before and after BCG and eye blink artifact removal. Shown are grand average stimulus-locked curves at Fz, from 500 ms pre-stimulus to 2000 ms post-stimulus for oddball (pink) and standard (green) stimuli. (Top) ERP before artifact removal. (Bottom) ERP after artifact removal. Horizontal axis is time in ms, and vertical axis is voltage in uV, with shaded bands indicating standard error across subjects (N = 19). Dark grey line at the bottom indicate if there is significant difference between evoked responses of different types of stimuli.
Figure 6.2: ERP at electrode Cz before and after BCG and eye blink artifact removal. Shown are grand average stimulus-locked curves at Cz, from 500 ms pre-stimulus to 2000 ms post-stimulus for oddball (pink) and standard (green) stimuli. (Top) ERP before artifact removal. (Bottom) ERP after artifact removal. Horizontal axis is time in ms, and vertical axis is voltage in uV, with shaded bands indicating standard error across subjects ($N = 19$). Dark grey line at the bottom indicate if there is significant difference between evoked responses of different types of stimuli.
Figure 6.3: ERP at electrode Pz before and after BCG and eye blink artifact removal. Shown are grand average stimulus-locked curves at Pz, from 500 ms pre-stimulus to 2000 ms post-stimulus for oddball (pink) and standard (green) stimuli. (Top) ERP before artifact removal. (Bottom) ERP after artifact removal. Horizontal axis is time in ms, and vertical axis is voltage in uV, with shaded bands indicating standard error across subjects ($N = 19$). Dark grey line at the bottom indicate if there is significant difference between evoked responses of different types of stimuli.
Figure 6.4: Evoked pupil dilation. Grand average stimulus-locked curves from 500 ms pre-stimulus to 2000 ms post-stimulus for oddball (pink) and standard (green) stimuli, with time on the horizontal axis and units of percentage change on the vertical axis, with shaded bands indicating standard error across subjects ($N = 19$). Dark grey line at the bottom indicate if there is significant difference between evoked responses of different types of stimuli.
CHAPTER 6. PUPIL-EEG-FMRI EXPERIMENT - UNI-MODAL

Figure 6.5: EEG classifier performance. Shown are cross-subject classifier performance as defined by area under the ROC curve. Horizontal axis is the time at the center of the sliding window, whereas vertical axis is the area under the ROC curve. Bold black line indicates average classifier performance, with colored line indicating classifier performances of individual subjects, and dashed line indicating a $p = 0.01$ Az value.

P300 component at the parietal site (Pz), peaking in the vicinity of 400 ms. These results are also consistent with what we observed in the simultaneous pupil-EEG experiment (see Figure 5.1).

6.2.5 Single-trial EEG analysis

With the single-trial EEG analysis approach (as discussed in Section 4.1), we evaluated our classifier’s performance first, as shown in Figure 6.5. Average Az value surpassed a substantial 0.75 threshold between 200 to 700 ms, consistent with previous findings in the simultaneous pupil-EEG project ($p < 0.01$ for $Az > 0.6$, shown in Figure 5.3).
6.2.6 Traditional fMRI analysis

The traditional fMRI analysis revealed a widely distributed network of areas showing greater BOLD responses for oddball than standard stimulus. Activations spread mainly across the parietal and frontal lobes, with one notable exception. Two groups of small activations were localized to the brainstem - one in the vicinity of the LC, and another near the inferior colliculus (IC), respectively.

Figure 6.6 illustrates the BOLD activations in the cortical regions, while Figure 6.7 illustrates the small activations we found in the brainstem. Table 6.1 provides a summary of the activations when using a traditional oddball > standard contrast. Note that all coordinates in the subsequent activation tables are in the MNI space.
Figure 6.7: Traditional fMRI analysis results at the brainstem. Activation maps showing greater BOLD response to oddball than standard stimulus. All results are of positive effect, and multiple comparison corrected with $z > 3.1$ and $p < 0.05$. X, Y, Z are MNI coordinates. BS, brainstem.
### Traditional Oddball > Standard Contrast

<table>
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<th>Contrast</th>
<th>Effect</th>
<th>(N_{\text{vox}})</th>
<th>(\text{Max}_Z)</th>
<th>(P_{\text{FWEC}}^{\text{clus}})</th>
<th>(X)</th>
<th>(Y)</th>
<th>(Z)</th>
<th>Region</th>
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<td>10</td>
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<tr>
<td></td>
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<td>567</td>
<td>5.59</td>
<td>2.71E-09</td>
<td>-30</td>
<td>44</td>
<td>30</td>
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<tr>
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<td>0.0332</td>
<td>26</td>
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<td>7.75E-07</td>
<td></td>
<td>-20</td>
<td>38</td>
<td>50</td>
<td>Superior Frontal Gyrus, Frontal Pole, Middle Frontal Gyrus</td>
</tr>
</tbody>
</table>

**Table 6.1: BOLD correlates of oddball > standard contrast in traditional fMRI analysis.** Significant clusters resulting from traditional fMRI analysis. Effect column presents the sign of the effect, \(N_{\text{vox}}\) column presents the number of voxels in the specific cluster, \(\text{Max}_Z\) column presents the maximum z-score of the cluster, \(P_{\text{FWEC}}^{\text{clus}}\) column presents the cluster’s FWE corrected P-value, \(X\), \(Y\), and \(Z\) Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
6.3 Summary

The single modality pupillometry and EEG data analyses revealed results similar to that in the simultaneous pupil-EEG experiment. The timings of pupillary response and ERP components, as well as the overall EEG classifier performance were largely consistent with the previous experiment, indicating that the data acquired inside the MR scanner were not substantially different compared to that collected in a non-MR environment.

The traditional fMRI analysis revealed a widespread network of activations in frontal and parietal areas. Specifically, we found regions where BOLD responses are larger for oddball than standard in the inferior parietal lobule (IPL), superior temporal gyrus (STG), Heschl’s gyrus, and middle frontal gyrus (MFG). Activations found in the postcentral gyrus were left-lateralized, demonstrating the effect of subjects’ behavioral response with the right hand. These findings were largely consistent with previous work [Stevens et al., 2000, Walz et al., 2014].

In addition to activations in the cortical regions, two groups of small activations were found in the brainstem. The first group of activations, located at [4, -32, -18] in MNI coordinates, is in the vicinity of the locus coeruleus (per coordinate reported by [Keren et al., 2009]). The second group of activations, located at [8, -30, -15], is close to the location of the inferior colliculus (per coordinates reported by [Kim et al., 2017]). As the IC receives dense projections from LC, and is part of the ascending auditory pathway, activations near the IC suggest the subcortical region’s sensitivity to auditory stimulus manipulation [Joshi et al., 2016]. Taken together with the activations near LC, these findings have the potential of inferring the role of arousal from the brainstem to the cortical regions.

However, we cannot conclude that the above observed activations in the brainstem are localized to the locus coeruleus or the inferior colliculus. This is because 1) subcortical BOLD signals can be strongly affected by sources of physiological noise [Murphy et al., 2014], and 2) the spatial smoothing step in fMRI data pre-processing allows the contribution of adjacent voxels to the estimated signal, therefore causing blurring in smaller features [Poldrack et al., 2011]. As the brainstem is a subcortical region located relatively deep inside the brain, the detection of functional signal and subsequent activations associated with this area is usually limited both in its amplitude and spatial extent. Such small scale activations are therefore more susceptible to the filtering effect of spatial smoothing. Additional steps are therefore necessary to exclude the potential factors of signal con-
tamination, in order to ensure the robustness of the observed effects [Poldrack et al., 2011, Murphy et al., 2014].
Chapter 7

Simultaneous pupil-EEG-fMRI experiment: combined pupil-EEG analysis

7.1 Introduction

This chapter discusses the analysis based on the combination of pupil and EEG data collected in the MR scanner environment. We examine the relationship between pupil and EEG trial-to-trial variability once again, followed by a discussion on some of the new findings compared to that in the simultaneous pupil-EEG experiment.

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.2 and 4.4.

7.2 Results

To begin with, Figure 7.1 illustrates the strong relationship between $\tilde{y}$ and RT, which justifies the need to regress out RT from the EEG discriminating component - as we are interested in the variability in the latent states that is not explainable by RT.

Somewhat contrary to what we observed in the pupil-EEG experiment, in the pupil-EEG-fMRI experiment, we did not find significant negative linear relationship between PDB and EEG discrim-
Figure 7.1: GLM fit of original $\hat{y}$ vs. RT. Horizontal axis is time in ms, vertical axis is the value of the parameter estimate. Dark grey line represents the parameter estimate for linear relationship, while light grey line represents the parameter estimate for quadratic relationship. Dark grey dots indicate windows at which the parameter estimate is significant for linear fit, while light grey dots indicate windows at which the parameter estimate is significant for quadratic fit.
Figure 7.2: GLM fit of residual $\tilde{y}$ vs. PDB. Horizontal axis is time in ms, vertical axis is the value of the parameter estimate. Dark grey line represents the parameter estimate for linear relationship, while light grey line represents the parameter estimate for quadratic relationship. Light grey dots indicate windows at which the parameter estimate is significant for quadratic fit.

Identifying components (the linear fit between PDB and an early window (275 ms) EEG discriminating component did approach the significant threshold though didn’t surpass it). Instead, we observed a positive quadratic (and likely negative linear) relationship between PDB and late window (475 to 525 ms) EEG STV discriminating component, as shown in Figure 7.2. A positive linear relationship which was not seen in the simultaneous pupil-EEG experiment was found for the PR and middle window (350 ms) EEG STV discriminating component, as shown in Figure 7.3. Additionally, when examining pairwise relationship between measures of interest, we observed a significant relationship only between PDB and PR, as shown in Figure 7.4.
Figure 7.3: GLM fit of residual \( \tilde{y} \) vs. PR. Horizontal axis is time in ms, vertical axis is the value of the parameter estimate. Dark grey line represents the parameter estimate for linear relationship, while light grey line represents the parameter estimate for quadratic relationship. Dark grey dots indicate windows at which the parameter estimate is significant for linear fit.
Figure 7.4: Pairwise GLM fit between measures of interest. Horizontal axis is GLM fits between different measures of interest, vertical axis is the value of the parameter estimate, with standard error computed across subjects ($N = 19$). Dark grey bars represents the parameter estimate for linear relationship, while light grey bars represents the parameter estimate for quadratic relationship. Significant correlations ($p < 0.05$) are denoted by single asterisks, with dashed line at zero correlation.
7.3 Summary

Our results from the simultaneous pupil-EEG-fMRI experiment exhibit some deviation from our previous findings in the simultaneous pupil-EEG experiment. First, in the simultaneous pupil-EEG experiment, we observed a negative linear relationship between PDB and both early window (175 to 200 ms) and middle window (375 to 400 ms) EEG component variability. In the current pupil-EEG-fMRI experiment, however, we found that PDB exhibited a quadratic relationship with late window (475 to 525 ms) EEG variability. Additionally, PR demonstrated a positive linear relationship with middle window (350 ms) EEG variability, which was absent from our previous experiment.

The above differences between the results from our two experiments likely reflected the differences in the experimental conditions and the data pre-processing and analysis approaches. Consequently, we believe that the correlations we see in this chapter still provides a truthful representation of the relationship between pupil-linked arousal and neural processes related with attention reorienting. Nevertheless, in the final discussion chapter, we will present a more in-depth discussion on the possible causes of such discrepancies.
Chapter 8

Simultaneous pupil-EEG-fMRI experiment: combined EEG-fMRI analysis

8.1 Introduction

For the next three chapters, we will continue to examine the relationship between data recorded from different modalities - specifically, with fMRI acquired BOLD signal always being the response variable, and pupillary or EEG or a combination of the two features being the explanatory variables.

In the current chapter, we begin with EEG-fMRI dual modality analysis. As demonstrated in previous chapters, with its millisecond temporal resolution, EEG is capable of investigating neural activity on a fine time scale. The spatial resolution of this recording modality, however, is not as satisfactory. In fact, EEG measures a spatial mixture of the underlying cortical activity and therefore provides only limited spatial resolution [Debener et al., 2006]. fMRI, on the other hand, enables brain regions engaged during cognitive processes to be localized with high spatial precision, although the slow response of the BOLD signal is not fast enough to capture fully the rich temporal dynamics that underlie cognitive processes [Debener et al., 2006]. EEG and fMRI therefore provide complementary advantages with regard to the temporal and spatial resolution of brain activity, especially when acquired concurrently [Debener et al., 2006, Debener et al., 2008].
In this dual modality analysis, we aim to identify brain regions sensitive to the trial-to-trial variability of temporally specific neural processes. Specifically, we used the poststimulus EEG discriminating component to inform fMRI analysis, and demonstrated that with STV of the EEG component, variabilities in the BOLD signal can be temporally localized.

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.2 and 4.4.

8.2 Results

The EEG component STV informed fMRI analysis revealed a network of regions associated with EEG discriminating component of different poststimulus windows (as shown in Tables 8.1, 8.2, 8.3, and 8.4). Areas from the visual cortex, precentral gyrus (PreCG), superior parietal lobule, and postcentral gyrus all correlated positively with early window (225 to 300 ms) EEG variability. Starting from middle window (350 to 425 ms), EEG variability were correlated with areas in the precuneus and cuneus cortices, as well as an abundance of regions in the prefrontal cortex. Towards the end of the trial, the anterior cingulate cortex, supplementary motor area (SMA), frontal operculum (FOL), and central operculum (COL) covaried with the EEG variability. It is worth noting that the sign of effect switched around the time of the P300 ERP component: correlation between BOLD and EEG variability started positive, then drifted towards negative as the trial progressed. Figure 8.1, 8.2, 8.3, 8.4 illustrate a selection of the activations described above.

8.3 Summary

The results of our EEG-fMRI dual modality analysis demonstrate that using STV of EEG discriminating component, variabilities in the BOLD signal can be temporally localized. In other words, EEG variability of different windows can be used to assign temporal order to associated brain regions, facilitating inferences to be made on the areas that may be associated with neural processes spanning the trial.
Figure 8.1: EEG STV informed fMRI analysis results located at the superior parietal lobule. Activation maps showing significant BOLD response specific to oddball EEG STV at 225 ms. All results are of positive effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. $X$, $Y$, $Z$ are MNI coordinates. SPL, superior parietal lobule.
Figure 8.2: EEG STV informed fMRI analysis results located at the anterior cingulate cortex. Activation maps showing significant BOLD response specific to oddball EEG STV at 425 ms. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. ACC, anterior cingulate cortex.
Figure 8.3: EEG STV informed fMRI analysis results located at the anterior cingulate cortex. Activation maps showing significant BOLD response specific to oddball EEG STV at 600 ms. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. ACC, anterior cingulate cortex.
CHAPTER 8. PUPIL-EEG-FMRI EXPERIMENT - BI-MODAL II

Figure 8.4: EEG STV informed fMRI analysis results located at the frontal operculum. Activation maps showing significant BOLD response specific to oddball EEG STV at 600 ms. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. FOL, frontal operculum. ACC, anterior cingulate cortex.
## EEG-fMRI GLM - Oddball EEG-STV modulated Regressor

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Effect</th>
<th>$N_{\text{vox}}$</th>
<th>Max$_Z$</th>
<th>$P_{\text{FWE}}^{\text{clus}}$</th>
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<th>Y</th>
<th>Z</th>
<th>Region</th>
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<td>64</td>
<td>Superior Parietal Lobule, Lateral Occipital Cortex, superior division</td>
</tr>
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</table>

### Table 8.1: BOLD correlates of oddball EEG-STV regressor in EEG-STV modulated fMRI analysis.

Significant clusters resulting from window centers $\leq$ 250 ms EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, Max$_Z$ column presents the maximum $z$-score of the cluster, $P_{\text{FWE}}^{\text{clus}}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak $z$-score, and Region column presents the regions associated with the cluster.
### EEG-fMRI GLM - Oddball EEG-STV modulated Regressor

<table>
<thead>
<tr>
<th>Contrast</th>
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<th>Max\textsubscript{Z}</th>
<th>$P_{FWE}^{\text{plus}}$</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Region</th>
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<td>-26</td>
<td>52</td>
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</tr>
<tr>
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<td>-94</td>
<td>22</td>
<td>Occipital Pole</td>
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<tr>
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<td>-44</td>
<td>62</td>
<td>Superior Parietal Lobule, Postcentral Gyrus</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Gyrus, Superior Parietal Lobule</td>
</tr>
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</table>

**Table 8.2: BOLD correlates of oddball EEG-STV regressor EEG-STV modulated fMRI analysis.**

Significant clusters resulting from $275 \text{ ms} \leq \text{window center} \leq 375 \text{ ms}$ EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, $N\text{vox}$ column presents the number of voxels in the specific cluster, Max\textsubscript{Z} column presents the maximum z-score of the cluster, $P_{FWE}^{\text{plus}}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
### EEG-fMRI GLM - Oddball EEG-STV modulated Regressor

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Effect</th>
<th>$N_{\text{vox}}$</th>
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<th>$P^{\text{clus}}_{\text{FWE}}$</th>
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<th>Y</th>
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<td>-60</td>
<td>50</td>
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<td>60</td>
<td>Superior Frontal Gyrus, Frontal Pole</td>
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<td>Negative (-)</td>
<td>544</td>
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<td>52</td>
<td>Lateral Occipital Cortex, superior division, Precuneous Cortex</td>
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**Table 8.3: BOLD correlates of oddball EEG-STV regressor in EEG-STV modulated fMRI analysis.**

Significant clusters resulting from $375 \text{ ms} \leq \text{ window center} \leq 400 \text{ ms}$ EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, Max $Z$ column presents the maximum $z$-score of the cluster, $P^{\text{clus}}_{\text{FWE}}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak $z$-score, and Region column presents the regions associated with the cluster.
## EEG-fMRI GLM - Oddball EEG-STV modulated Regressor

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Effect</th>
<th>( N_{\text{vox}} )</th>
<th>MaxZ</th>
<th>( P_{FWE}^{\text{clus}} )</th>
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<th>Y</th>
<th>Z</th>
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<td>Superior Frontal Gyrus, Paracingulate Gyrus, Supplementary Motor Cortex</td>
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<td>395</td>
<td>3.35</td>
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<td>Negative (-)</td>
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<td>16</td>
<td>-6</td>
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</table>

Table 8.4: BOLD correlates of oddball EEG-STV regressor in EEG-STV modulated fMRI analysis. Significant clusters resulting from window centers \( \geq 425 \text{ ms} \) EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, \( N_{\text{vox}} \) column presents the number of voxels in the specific cluster, MaxZ column presents the maximum z-score of the cluster, \( P_{FWE}^{\text{clus}} \) column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
8.3.1 Temporal order of observed activations

Notably, the activations exhibited a sequential order which began with SPL, followed by frontal pole and ACC, before concluding with ACC and frontal operculum at 600 ms into the trial. In more specific terms, the SPL activations related with early window EEG variability suggest an active role of the task-relevant region in re-orienting, as proposed in previous publication [Corbetta et al., 2008]. Activations in the prefrontal area provide evidence for a functional link between such regions and middle window EEG variability, consistent with previous findings [Walz et al., 2013]. Lastly, the fact that ACC and FOL were activated in late time window of the trial, points towards a potential link between post behavioral response related neural processes to the medial prefrontal cortex (mPFC).

Taken together, our findings painted a temporally and spatially specific network which holds the potential of explaining interactions between different cortical and subcortical systems related with attention reorienting. In the next chapters, we will continue to investigate such interplays using data from different modality combinations.
Chapter 9

Simultaneous pupil-EEG-fMRI experiment: combined pupil-fMRI analysis

9.1 Introduction

After investigating how pupil-linked arousal and temporally specific neural processes inferred by EEG discriminating components covary in Chapter 7, and the spatial correlates of such EEG components in Chapter 8, we examine the brain regions correlated with different levels of pupil-linked arousal, with the combination of pupil and fMRI data in this chapter. Specifically, we used both the prestimulus and poststimulus pupillary measures to inform fMRI analysis, and present some of the first evidence on how baseline and event-evoked pupil size may relate to attention reorienting driven brain regions. With PDB and PR indexing the tonic and phasic activity level of LC, respectively, our results hold the potential of deciphering how different levels of arousal interact with cortical regions engaged in an attention reorienting task.

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.2 and 4.4.
Figure 9.1: PDB STV informed fMRI analysis results located at the anterior cingulate cortex. Activation maps showing significant BOLD response specific to oddball PDB STV. All results are of positive effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. SMG, supramarginal gyrus. ACC, anterior cingulate cortex.

9.2 Results

The pupillary measures STV informed fMRI analysis revealed a network of regions associated with either the PDB or the evoked PR (as shown in Tables 9.1, and 9.2). The frontal pole (FPO) and ACC showed correlations with oddball PDB STV, while the superior parietal lobule, inferior frontal gyrus (IFG), and supramarginal gyrus (SMG) exhibited correlations with oddball PR STV. Interestingly, PDB STV showed both positive and negative effects, whereas PR STV was only positively correlated with corresponding brain regions. Figure 9.1, 9.2, 9.3, 9.4, and 9.5 illustrate a selection of the activations described above.
Figure 9.2: PDB STV informed fMRI analysis results located at the frontal pole. Activation maps showing significant BOLD response specific to oddball PDB STV. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. FPO, frontal pole. LOC, lateral occipital cortex. OPO, occipital pole.
Figure 9.3: PR STV informed fMRI analysis results located at the superior parietal lobule. Activation maps showing significant BOLD response specific to oddball PR STV. All results are of positive effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. lSPL, left superior parietal lobule. rSPL, right superior parietal lobule. SFG, superior frontal gyrus. PreCG, precentral gyrus. MFG, middle frontal gyrus. FPO, frontal pole. OFC, orbitofrontal cortex.
Figure 9.4: PR STV informed fMRI analysis results located at the inferior frontal gyrus. Activation maps showing significant BOLD response specific to oddball PR STV. Blue regions indicate negative effect. All results are of positive effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. lIFG, left inferior frontal gyrus. rIFG, right inferior frontal gyrus. FPO, frontal pole. lPOL, left parietal operculum. rPOL, right parietal operculum. V1, visual cortex. SMG, supramarginal gyrus. MFG, middle frontal gyrus. STG, superior temporal gyrus. PreCG, precentral gyrus. SMA, supplementary motor area. SFG, superior frontal gyrus. COL, central operculum.
Figure 9.5: PR STV informed fMRI analysis results located at the supramarginal gyrus. Activation maps showing significant BOLD response specific to oddball PR STV. Blue regions indicate negative effect. All results are of positive effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. lSMG, left supramarginal gyrus. rSMG, right supramarginal gyrus. FPO, frontal pole. IFG, inferior frontal gyrus. PreCG, precentral gyrus. PoCG, postcentral gyrus. STG, superior temporal gyrus.
Table 9.1: BOLD correlates of oddball pupil diameter baseline STV regressor in pupil-STV modulated fMRI analysis. Significant clusters resulting from pupil diameter baseline STV modulated fMRI analysis. Effect column presents the sign of the effect, $N_{\text{vox}}$ column presents the number of voxels in the specific cluster, MaxZ column presents the maximum z-score of the cluster, $P_{\text{FWE}}^{\text{clus}}$ column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
### Pupil-fMRI GLM - Oddball PR STV modulated Regressor

<table>
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<th>Contrast</th>
<th>Effect</th>
<th>N&lt;sub&gt;vox&lt;/sub&gt;</th>
<th>Max Z</th>
<th>P&lt;sub&gt;clus FWE&lt;/sub&gt;</th>
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<th>Y</th>
<th>Z</th>
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<td>40</td>
<td>Supramarginal Gyrus, posterior division,</td>
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<td>1158</td>
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<td>8</td>
<td>16</td>
<td>Inferior Frontal Gyrus, pars opercularis, Pre-central Gyrus</td>
</tr>
</tbody>
</table>
9.3 Summary

To the best of our knowledge, the findings we present in this chapter constitute some of the first evidence in differentiating brain regions correlated with baseline pupil-linked arousal apart from those correlated with event-related pupil-linked arousal in an attention reorienting task.

9.3.1 Spatial correlates of tonic pupil-linked arousal

PDB STV were correlated with variability of the BOLD signal in the frontal pole and anterior cingulate cortex. Mounting evidence has supported the feasibility of using pupil diameter to index LC activity [Aston-Jones and Cohen, 2005, Murphy et al., 2014], which confirms that using pupillary measures to infer tonic and phasic LC activity is legitimate. With PDB STV indexing the variability of tonic LC activity, its correlation with the ACC lends additional support to the physiological link between the two structures - as LC-NE system receives cortical input from the anterior cingulate [Aston-Jones and Cohen, 2005]. The correlation between PDB STV and frontal pole, on the other hand, suggests a potential functional link between the default and arousal systems.

9.3.2 Spatial correlates of phasic pupil-linked arousal

PR STV, on the other hand, correlated with the superior parietal lobule, inferior frontal gyrus, and supramarginal gyrus. The connection between PR STV and BOLD signal variability in SPL is expected, as the latter is involved in the dorsal attention network, which is responsible for initiating attention reorienting. Activations in the IFG and SMG, on the other hand, point towards the possibility of a functional relationship between phasic pupil-linked arousal and the ventral attention network.

Taken together, our results indicate that phasic pupil-linked arousal is likely to be related to both the dorsal and ventral attention networks, suggesting active roles of both networks when actively engaged in the task. The relationship between PDB STV and prefrontal regions, however, might indicate a constant monitoring of the cortical states stemmed from the neuromodulatory system. In the next chapter, we will combine all three modalities to make inferences on the potential location where interaction between arousal and attention networks might have taken place.
Chapter 10

Simultaneous pupil-EEG-fMRI experiment: triple modality analysis

10.1 Introduction

Taken together, findings from the dual modality analyses discussed in previous chapters (Chapters 7, 8, and 9) enabled the following inferences - baseline pupil-linked arousal is temporally linked to late window (475 to 525 ms) EEG variability, and spatially linked to the prefrontal regions. Event-related pupil-linked arousal, on the other hand, is temporally related to middle window (350 ms) EEG variability, and spatially related to task-relevant regions in both the dorsal and ventral attention networks. It is therefore tempting to conclude that the interaction between different levels of arousal and temporally specific neural components indeed took place in the regions observed above.

In fact, one of the subtleties of cross modality analyses, is the possibility that covariation in the pairwise modality analyses may point to neural activity of different sources. For instance, the fact that event-related pupil-linked arousal is 1) linked to middle window EEG variability, and 2) also linked to task-relevant regions does not provide sufficient evidence to conclude that event-related pupil-linked arousal interacts with neural processes around middle window, and this interaction is expressed in task-relevant regions. It is possible that these two links simply stemmed from different pathways, and shall therefore be treated independently. What additional information, or more specifically, what kind of multimodal integration, can then shed more light on where the
interaction between pupil-linked arousal and neural processes actually might have taken place?

In this chapter, we aim to answer this question with preliminary results from fusing data across all three modalities. Contrary to pairwise modality analyses, which incorporated two modalities in the analyses, we discuss our approach in combining information from all three modalities to make inferences. More importantly, we demonstrate how a meaningful combination of data not only provides more interpretability, but also unique specificity to the results.

For the pre-processing and analysis approaches utilized in this analysis, refer to Sections 3.1.2 and 4.4.

10.2 Results

In addition to the interaction analysis, we first performed a simple comparison analysis on spatial correlates related to PR STV, and spatial correlates of a middle window (350 ms) EEG component variability. Figure 10.1 illustrates the activations related with each STV, as well as the overlapping regions. The overlap occurred at SPL and PoCG, as indicated by the yellow regions in Figure 10.1.

With respect to the interaction analysis, oddball PDB x EEG variability correlated with a variety of regions (Table 10.1). The middle frontal gyrus, middle and inferior temporal gyrus (MTG, ITG respectively), the precuneus cortex, the superior lateral occipital cortex, and the angular gyrus all showed correlations with the PDB x EEG interaction term. Figure 10.2 and 10.3 illustrate the activations described above.

10.3 Summary

10.3.1 Combination of dual modality analysis results

The first triple modality analysis illustrates the additional explanatory power brought in by a complete combination of results from each dual modality analysis. Specifically, linkage between event-related PR and middle window EEG variability is likely to be expressed in task-relevant regions like the superior parietal lobule and postcentral gyrus.

Specifically, with pupil-EEG analysis, the correlation between PR and middle window (350 ms) EEG variability is uncovered, as shown in Figure 7.3. With EEG-fMRI analysis, the correlation
CHAPTER 10. PUPIL-EEG-FMRI EXPERIMENT - TRI-MODAL

Figure 10.1: Overlap of PR and EEG STV informed fMRI analysis results located at the superior parietal lobule. Activation maps showing significant BOLD response specific to oddball PR STV (red), EEG STV at 350 ms (green), and the regions that overlap (yellow). All regions exhibit positive effect. Results are multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. lPoCG, left postcentral gyrus. SPL, superior parietal lobule. SFG, superior frontal gyrus. SMA, supplementary motor area. PreCG, precentral gyrus. rSPL, right superior parietal lobule. FOL, frontal operculum. lSMG, left supramarginal gyrus. rSMG, right supramarginal gyrus. STG, superior temporal gyrus.
Figure 10.2: PDB and EEG STV informed fMRI analysis results located at the precuneus cortex. Activation maps showing significant BOLD response specific to the interaction term of oddball PDB and EEG STV at 525 ms. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. PCUN, precuneus cortex. LOC, lateral occipital cortex. MFG, middle frontal gyrus. MTG, middle temporal gyrus.
Figure 10.3: PDB and EEG STV informed fMRI analysis results located at the middle frontal gyrus. Activation maps showing significant BOLD response specific to the interaction term of oddball PDB and EEG STV at 525 ms. All results are of negative effect and multiple comparison corrected with $z > 2.3$ and $p < 0.05$. X, Y, Z are MNI coordinates. MFG, middle frontal gyrus. LOC, lateral occipital cortex.
### Pupil x EEG-fMRI GLM - Oddball PDB x EEG 525ms STV modulated Regressor

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<td>527</td>
<td>3.58</td>
<td>7.04E-04</td>
<td>38</td>
<td>-62</td>
<td>56</td>
<td>Lateral Occipital Cortex, superior division, Angular Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>471</td>
<td>3.55</td>
<td>1.71E-03</td>
<td>-18</td>
<td>-50</td>
<td>36</td>
<td>Precuneous Cortex, Cingulate Gyrus, posterior division</td>
</tr>
<tr>
<td></td>
<td></td>
<td>418</td>
<td>3.34</td>
<td>4.11E-03</td>
<td>40</td>
<td>6</td>
<td>46</td>
<td>Middle Frontal Gyrus, Precentral Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>334</td>
<td>3.82</td>
<td>1.78E-02</td>
<td>58</td>
<td>-54</td>
<td>-10</td>
<td>Middle Temporal Gyrus, tempororooccipital part</td>
</tr>
</tbody>
</table>

Table 10.1: BOLD correlates of oddball PDB x EEG STV regressor in oddball pupil diameter baseline x EEG-STV modulated fMRI analysis. Significant clusters resulting from PDB x 525ms Oddball EEG-STV modulated fMRI analysis. Effect column presents the sign of the effect, N<sub>vox</sub> column presents the number of voxels in the specific cluster, Max<sub>Z</sub> column presents the maximum z-score of the cluster, P<sub>clus</sub><sub>FWE</sub> column presents the cluster’s FWE corrected P-value, X, Y, and Z Coordinates column present the location with peak z-score, and Region column presents the regions associated with the cluster.
between middle window EEG variability and SPL and postcentral gyrus is discovered, similar to what is shown in Figure 8.1. And with pupil-fMRI analysis, the correlation between PR and SPL and postcentral gyrus is revealed, as shown in Figure 9.3. As shown in Figure 10.1, the SPL and postcentral gyrus overlap between dual modality results is clearly visible. This finding implies that PR, and therefore the phasic LC activity it’s indexing, likely interacts with regions both in the primary somatosensory cortex and dorsal attention network on an early to middle window timescale.

Recall that in the beginning of this chapter, we used the above discussed dual modality results to demonstrate the challenge in confirming interaction in a multi-modality analysis. Such challenge, however, can be resolved by the findings above, as we have successfully linked each modality to the other. In more specific terms, we have demonstrated that 1) PR is linked to EEG component at a middle window time (350 ms), 2) that exact EEG component is linked to regions in the primary somatosensory cortex and dorsal attention network (postcentral gyrus and SPL), 3) those exact regions in turn are linked with PR. In other words, such findings serve as a validation towards previous inferences, suggesting that phasic pupil-linked arousal and activations in the somatosensory cortex might indeed reflect interaction between pupil-linked arousal and dorsal network in middle window stages of sensory information processing.

10.3.2 Integration of cross modality STV

In addition to the comparison approach we adopted in the first triple modality analysis, the second triple modality analysis creates a true interaction term with both pupil and EEG STV measures, before feeding this term in the regression analysis to inform BOLD correlates of such interaction. Our efforts uncovered that the interaction between PDB and late window EEG variability is expressed in regions such as the superior lateral occipital cortex, precuneus cortex and middle frontal gyrus. More importantly, this relationship cannot be inferred from dual modality analyses alone. The absence of such inference from dual modality analyses could be further illustrated as 1) PDB is linked to EEG component at a late window time (525 ms), 2) that exact EEG component is not linked to any region in the combined EEG-fMRI analysis, and 3) PDB is linked to lateral occipital cortex and cingulate cortex, while neither MFG or the precuneus cortex was present in the BOLD correlates of PDB.
In other words, using an interaction term which combines pupil and EEG variability achieves the tuning of the whole-brain analysis. This combined variability is therefore capable of identifying the locations which may be related with the interactions between internal arousal states and neural processes.

Specifically, activations in the precuneus cortex could lead to one possible interpretation, that there is interaction between the tonic activity of LC and the default mode network (DMN). This potential modulation from the LC-NE system might indicate a shift along the tonic arousal continuum, likely reflected as shifting from task engaged to slight drowsiness or increased tendency for exploration.

In the following final chapter, we will discuss the above and all previous findings with respect to the literature, and demonstrate the originality and impact of our results.
Chapter 11
Discussion

This chapter concludes this dissertation with a brief overview of the novel contribution of our work, followed by a final discussion on the major findings. In each discussion section, we will first present an overview of relevant work in the field, followed by the additional or alternative interpretations our results could offer, in explaining the spatiotemporal dynamics of the pupil-linked arousal and reorienting systems.

11.1 Novel contribution

The act of attention reorienting, trivial as it may seem, constitutes one of the most critical functions for both animals and humans to safely interact with the environment [Corbetta et al., 2008]. Such reorienting calls for an intricate set of adjustments in response to novel and unexpected stimuli [Corbetta et al., 2008]. Previous work indicates that this adaptive behavior may involve a complex interaction between cortical systems specialized for the selection of sensory information, with more recent work suggesting arousal, as another potential contributor to the brain’s activations related to unexpected stimuli [Corbetta et al., 2008].

A rich body of work has since been devoted to investigating the relationship between the reorienting and arousal systems in humans in the recent years, with increasing interest in concurrent cross modality analysis. While these studies have undoubtedly furthered our understanding of how one system may interact with the other, the data integration approach has remained almost exclusively pairwise (using a combination of pupil-EEG, EEG-fMRI, or pupil-fMRI recordings), and
likely lacks revealing power when compared with a simultaneous triple modality (i.e. a concurrent pupil-EEG-fMRI) analysis.

In this thesis, we demonstrate that it is worthwhile to exploit the potential of concurrent triple modality acquisition and analysis, especially when considering the power such approach could offer in discovering interpretable associations between neural systems of interests. We show that 1) the technical challenges notwithstanding, it is feasible to acquire data from all modalities with satisfactory SNR; 2) the preservation of trial-to-trial variability in data analysis gives one an edge in capitalizing the complementary information each of the three modalities entail, and in inferring the spatiotemporal dynamics of the pupil-linked arousal and reorienting systems with dual modality analysis; and 3) integrating single trial variabilities of all modalities together holds the potential of revealing brain regions where the interactions between pupil-linked arousal and reorienting systems might have taken place. More importantly, such regions were concealed from all previous dual modality analyses conducted in this thesis, demonstrating the unique specificity and revealing power of our triple modality analysis.

11.2 Discussion of major findings

11.2.1 Combined pupil-EEG analysis: highlights the timing of potential interactions between systems

Relevant literature

[Murphy et al., 2011] first examined the relationship between LC activity (indexed by pupillary measures) and scalp EEG, by employing an auditory oddball task. They found that intermediate levels of tonic pupil diameter, accompanied by phasic pupil dilation in response to task-relevant stimuli, were associated with better performance than both low and high tonic pupil diameters, which were associated with diminished phasic responses. Recent work by [Kamp and Donchin, 2015] investigated the relationship between pupil-linked arousal and poststimulus ERPs, by correlating the pupil dilation response with P3 and novelty P3. They found that even when dissociating different subcomponents in the P3, such as responses to deviance (rare events on a categorical level) and novelty (of a particular item), the pupil response does not correlate with either on a trial-by-trial basis and thus seems to signal complementary information [Kamp and Donchin,
Together with the work of [Murphy et al., 2011], these findings suggest that P3 and pupil size may have complementary relations to LC-NE activity and thus together may index phasic and tonic LC activation during continuous task performance [Einhäuser, 2017].

Deviations from previous findings

Our results from the simultaneous pupil-EEG-fMRI experiment exhibit some deviations from both our own previous findings and other relevant studies. First, in the simultaneous pupil-EEG experiment, we observed a negative linear relationship between PDB and both early window (175 to 200 ms) and middle window (375 to 400 ms) EEG component variability. In the current pupil-EEG-fMRI experiment, however, we found that PDB exhibited a quadratic relationship with late window (475 to 525 ms) EEG variability. Additionally, PR demonstrated a positive linear relationship with middle window (350 ms) EEG variability, which was absent from our previous experiment, and the studies described above.

When compared with our own previous experiment, one of the explanations for the absence and emergence of previously unseen correlations is the distinctly different data acquisition environments. The audible MR scanner noise in simultaneous pupil-EEG-fMRI recording, for instance, constitutes one of the major factors that could affect a participant’s performance. It is possible that such influence could be reflected in different patterns of brain activity [Debener et al., 2006] - the visibly larger evoked PR in Figure 5.2 compared to that in Figure 6.4 seems to support this hypothesis.

The distinction between our current findings and those of [Murphy et al., 2011, Kamp and Donchin, 2015], on the other hand, may have stemmed from differences in experimental design and data analysis approaches. In terms of experimental design, the subjects performed a 37-min auditory oddball task without break in [Murphy et al., 2011]. This setup is more likely to induce drowsiness and encourage the subject’s arousal level to shift towards the left side of the Yerkes-Dodson curve. Such experimental manipulation might be able to capture levels of arousal that are different from ours, as our recording was broken up into 5 minute blocks of data collection, allowing the subject to rest in between. Meanwhile, in terms of different data analysis, [Kamp and Donchin, 2015] extracted EEG features with virtual ERPs derived from principal component analysis (PCA), contrary to our decomposition which is related to the task.
Inferences from current findings

Deviations from previous findings notwithstanding, our results provide additional evidence on the coupling between pupil-linked arousal and attention reorienting related neural processes. The presence of a positive relationship between middle window (350 ms) EEG variability and PR implies that stimulus-driven pupil-linked arousal may be directly linked to neural processes in the temporal vicinity of the P300 ERP component. Such findings were absent from the analyses of previous studies [Murphy et al., 2011, Hong et al., 2014, Kamp and Donchin, 2015], although the MR scanner-based nature of our concurrent triple modality acquisition environment may have been a contributing factor towards such deviation. The presence of a quadratic relationship between late window (475 to 525 ms) EEG variability and PDB, on the other hand, indicates the prolonged effect of baseline pupil-linked arousal on neural processes even well after reaction time. This finding falls in line with the observation of [Urai et al., 2017] in a perceptual decision making task. After participants had made their choice, but before receiving feedback about the correctness of that choice, their pupil size indicated decision uncertainty [Urai et al., 2017]. These results hint at the probability that neuromodulatory systems such as the pupil-linked arousal system may modulate the elicitation of task-relevant cortical responses both during and after decision formation, implying the continuous global effect of arousal to the cortical regions well into the process of reorienting.

Taken together, the results from this first dual modality analysis not only provided additional evidence on the coupling between pupil-linked arousal and attention reorienting related neural processes - more importantly, it provided critical timing information on where potential interactions between pupil-linked arousal and reorienting systems might have taken place. Such temporal localization not only facilitated following triple modality analyses as we no longer need to search blindly throughout the entirety of the trial, but also constituted the first layer of inferences for subsequent comprehensive spatiotemporal mappings between systems of interest.
11.2.2 Combined EEG-fMRI analysis: infers the coordinated dynamics of various cortical networks

Relevant literature

The practice of using trial-to-trial variability of EEG to correlate with concurrently recorded BOLD signal has been adopted by various previous studies [Debener et al., 2005, Eichele et al., 2005, Benar et al., 2007, Fuglo et al., 2012, Nguyen et al., 2014, Wirsich et al., 2014, Abreu et al., 2018]. Within the scenario of attention reorienting and especially oddball tasks, the most relevant work came from [Goldman et al., 2009, Walz et al., 2013, Walz et al., 2014]. [Goldman et al., 2009] examined the temporal progression of reorienting related neural processes within the context of an auditory oddball task, whereas [Walz et al., 2014] and [Walz et al., 2013] investigated such progressions with a visual and a combination of auditory and visual oddball tasks, respectively.

Specifically, [Goldman et al., 2009] found that the EEG STV during target detection strongly correlated with BOLD variability in the lateral occipital complex. Meanwhile, [Walz et al., 2013] found that the ACC correlated strongly with both early and late window EEG components, with [Walz et al., 2014] reporting activations in right-lateralized frontal regions and lateral occipital cortex when linking EEG component STV with that of the BOLD response.

Inferences from current findings

In the second dual modality analysis, we combined EEG discriminating component STV with fMRI data. The unique complementary information provided by each modality enabled us to localize system-specific brain regions that are correlated with trial-to-trial variability of neural processes at different poststimulus time. Intriguingly, in addition to the dorsal and ventral attention networks of the reorienting system, we also observed activations in the default mode network, suggesting a coordinated action spanning across various major cortical networks when reorienting is initiated and subsequently carried out.

Specifically, we found that the SPL, one of the core regions of the dorsal network, covaried with early window (225 to 300 ms) EEG variability. This is unsurprising as the dorsal network likely initiates the process of reorienting [Corbetta et al., 2008]. Additionally, correlations between the frontal pole and middle window EEG (350 to 400 ms) variability points to the possible involvement
of the default network in task-related processing. Previous work by [Walz et al., 2014] have also identified spatial correlates of neural components in the default network, albeit in a slightly later window as we observed here. One plausible explanation for the timing differences in activations localized in the default mode network, may be a discrepancy in the experimental paradigm. While [Walz et al., 2014] used a visual oddball paradigm, we used an auditory oddball paradigm so as to control for pupillometry related confounds. It is therefore possible that activations in the default network are expressed at different poststimulus offsets in relation to the type of sensory input one needs to process. Meanwhile, the lack of activations in the ventral network in our study may be a result of the differences in sensory input. This lack of activations might imply a variability difference in ventral network regions under different task conditions. The work of [Corbetta et al., 2008] and [Walz et al., 2014] both focused on visual tasks, which may elicit larger trial-to-trial variability in ventral network regions, compared to an auditory task as in our experiment. The lack of activation in ventral network regions in [Goldman et al., 2009] seems to support such an explanation.

Lastly, we observed a link between SMA as well as prefrontal regions like ACC and the frontal operculum with late window (600 ms) EEG variability. Neural components at such poststimulus latency have largely been unreported in relevant studies (i.e. those using an oddball paradigm, with the exception of [Walz et al., 2014]), especially with respect to the far more heavily studied N100, P200, and P300 components. Such emergence of activations, however, may further contribute towards the hypothesis that functional interactions between cortical reorienting and subcortical arousal systems exist. As the LC-NE system receives cortical input from the anterior cingulate [Aston-Jones and Cohen, 2005], the link between prefrontal regions like ACC with late window EEG variability coincide with an interpretation that the neuromodulatory system is involved in reorienting, and has a prolonged effect even after the behavioral response.

In summary, the results from the second dual modality analysis provided additional evidence on when and where the arousal and attention reorienting systems may covary with each other. Note that although our primary interest lies in the reorienting and arousal systems, activations observed in the default network implied that the reorienting response may indeed be expressed as a coordinated action of different cortical and subcortical systems, with each network or system accomplishing different aspects of such response (be it initiating, processing, constant monitoring or resetting).
11.2.3 Combined pupil-fMRI analysis: identifies the spatial locations of probable interactions between systems

Relevant literature

Compared with the combined pupil-EEG analysis which has a history approaching half a century, the combination of pupil-fMRI analysis is a relatively recent method. [Eckstein et al., 2017] provided a comprehensive review on recent pupil-fMRI work, which spans from task-related to resting-state relevant. One of the major recent studies, came from [Murphy et al., 2014]. The authors investigated the relationship between pupil diameter and BOLD activity localized to the human LC. Simultaneous pupillometry and fMRI revealed a relationship between continuous pupil diameter and BOLD activity in a dorsal pontine cluster overlapping with the LC, as localized via neuromelaninsensitive structural imaging and an LC atlas. This relationship was present both at rest and during performance of a two-stimulus oddball task, with and without spatial smoothing of the fMRI data, and survived retrospective image correction for physiological noise [Murphy et al., 2014]. Furthermore, the spatial extent of this pupil/LC relationship guided a volume-of-interest analysis in which the authors provide the first demonstration in humans of a fundamental characteristic of animal LC activity: phasic modulation by oddball stimulus relevance [Murphy et al., 2014].

In light of these advances, [Eckstein et al., 2017] proposed that pupil dilation reflects attentional focus and mental effort, and should therefore naturally correlate with the brain regions carrying out an attended task. In other words, pupil dilation and the activity of specific brain regions should be temporally coupled: as a task unfolds, arousal and mental effort reflected in pupil dilation may fluctuate. Such fluctuations are temporally coupled to the activity of implicated brain regions [Eckstein et al., 2017].

While [Murphy et al., 2014] reported relationship between LC activity and pupil size in a visual oddball task, their approach focused on a continuous pupillary measure down-sampled to the frequency of TR, and a subsequent volume-of-interest analysis localized to the LC. The trial-to-trial variability of pupillary features which could be reflective of the tonic and phasic modes of LC, however, did not result in significant correlations with cortical regions.

Our findings with the dual modality pupil-fMRI analysis, on the other hand, provide some of the first evidence on how baseline and stimulus-driven pupil-linked arousal may relate to attention
reorienting driven brain regions.

**Inferences from current findings**

The first and second dual modality analyses largely focused on the temporal and spatial mapping of neural processes involved in attention reorienting, with timing and region-specific information retrieved from EEG and fMRI, respectively. The third dual modality analysis, which combines pupillometry STV and BOLD signal, shifted the focus back to arousal, the candidate modulating factor of reorienting. This was achieved by identifying the spatial correlates of different levels of pupil-linked arousal, using PDB and PR to index the tonic and phasic pupil-linked arousal activity, respectively. To the best of our knowledge, the findings we present in this analysis also constitute some of the first evidence in differentiating brain regions correlated with baseline pupil-linked arousal apart from those correlated with stimulus-driven pupil-linked arousal in an attention reorienting task.

In more specific terms, we found that PDB STV were correlated with variability of the BOLD signal in the ACC and frontal pole, which provides additional support for the physiological link between the two structures - as LC-NE system receives top-down cortical input from the anterior cingulate [Aston-Jones and Cohen, 2005], and such input may in turn facilitate a bottom-up constant monitoring of the cortical states stemmed from the neuromodulatory system. We also found correlation between PR STV and variability of BOLD signal in the SPL, IFG, and SMG. Given that SPL is involved with the dorsal attention network, whilst IPG and SMG are involved with the ventral attention network, these findings indicate that phasic pupil-linked arousal is likely related to both the dorsal and ventral attention networks, adding further evidence towards the striking similarity between target-related responses in the ventral network, P300 potentials, and the phasic response in the LC [Corbetta et al., 2008].

**11.2.4 Combined pupil-EEG-fMRI analysis: creates a comprehensive spatiotemporal mapping of the interactions between systems**

**Relevant literature**

While interest in cross modality recording and analysis in cognitive neuroscience is accumulating, there is only one published human-based work where pupillometry, EEG, and fMRI were integrated
concurrently [Mayeli et al., 2019]. The authors recruited a small sample size (4 subjects in total), and used simultaneously recorded EEG, fMRI, and eye tracking to determine subject’s vigilance during a resting state fMRI [Mayeli et al., 2019].

In the final triple modality analyses, we integrated STV measures from all three modalities to infer the time and location where interactions between pupil-linked arousal and reorienting systems might have happened. Our findings constitute the first demonstration on what additional and unique information a triple modality recording and analyses could bring forth.

**Inferences from current findings**

To reiterate, while the pupil-EEG dual modality analysis temporally localized our focus to latencies where potential interactions between pupil-linked arousal and reorienting systems might occur, the EEG-fMRI dual modality analysis specifically examined the overall dynamics of these two systems, which allowed inferences to be made on regions which may be responsible of executing collectively exhaustive processes throughout different time windows of the reorienting response. The third pupil-fMRI dual modality analysis, subsequently, investigated the extent to which different levels of pupil-linked arousal may covary with various cortical regions - findings in this analysis in essence provide complementary spatial information on where the interactions between pupil-linked arousal and reorienting systems might have taken place.

In the context of triple modality analyses, the first analysis aims to exploit the findings from the three dual modality analyses using a simple combination approach. Much like in graph theory, measures from each modality could be viewed as a node, and the significant pairwise relationship between each modality-specific measure could be viewed as an edge in the graph. It is therefore possible to examine all three pairwise relationships at the same time by outlining the three nodes of a triangle first, and then investigate if edges between each pair of nodes exist. Specifically, measures from the pupillometry recording can be the prestimulus PDB or poststimulus PR, measures from the EEG recording can be EEG discriminating components at different poststimulus time, and measures from the fMRI recording can be BOLD signal at different brain regions.

For instance, as we have already temporally localized the timing at which potential interactions between phasic pupil-linked arousal and attention reorienting related neural processes may happen (with the dual modality pupil-EEG analysis), the first two nodes and the first edge of this triangle
have been confirmed (illustrated by the dotted line “A” in Figure 11.1): one node would be the measure of PR, indexing the stimulus-driven pupil-linked arousal; the other node would be the measure of EEG component at 350 ms poststimulus time. With dual modality EEG-fMRI analysis, we identified the cortical regions whose BOLD signal correlated with the EEG component for that exact middle window, therefore subsequently introduced the third node and the second edge of the triangle (illustrated by the dotted line “B” in Figure 11.1), with the spatial correlates for the 350 ms EEG component found specifically at the precentral and postcentral gyrus, and the SPL. Lastly, with dual modality pupil-fMRI analysis, we found that the BOLD signal in the SPL and postcentral gyrus once again covaried with the variability in the PR. Such finding essentially consolidated the last edge of the triangle (illustrated by the dotted line “C” in Figure 11.1), and provided definitive evidence on the time and location of the interactions between phasic pupil-linked arousal and neural processes near the timing of the P300 ERP component.

Figure 11.1 visualizes the above graph theory based discussion. The top section of the figure illustrates the connection between the LC-NE system and the pupil diameter, specifically the evoked PR (i.e. the first modality-specific node). On the left side of the figure, the EEG discriminating component at 350 ms poststimulus time is highlighted, and represents the second modality-specific node. Lastly, on the right side of the figure, spatial correlates of oddball PR and 350 ms EEG STV are shown inside the orange and purple boxes, respectively. The overlap between these two set of spatial correlates are highlighted in yellow, and is located at the SPL and postcentral gyrus. The significant relationships between each pair of measures are represented by the dotted line between each node. As discussed above, the presence of three solid edges enabled us to make inferences on the time and location of the interactions between pupil-linked arousal and poststimulus neural processes.

While a comparison based approach has its intuitive appeal, the lack of significant relationships between specific pairs of measures could make it more difficult to derive generalizable conclusions. For instance, the interactions between tonic pupil-linked arousal and attention reorienting related neural processes may happen at a relatively late window (475 to 525 ms), as inferred by the dual modality pupil-EEG analysis, once again outlining the first two nodes and the first edge of a new triangle (illustrated by the dotted line “A” in Figure 11.2): one node would be the measure of PDB, indexing the baseline pupil-linked arousal; the other node would be the measure of EEG
Figure 11.1: Illustration of interactions between phasic pupil-linked arousal and neural processes in the temporal vicinity of P300 ERP component. The top section of the figure illustrates the connection between the LC-NE system and the pupil diameter, specifically the evoked PR, with standard and oddball stimulus driven PRs colored in green and pink, respectively. The EEG discriminating component at 350 ms poststimulus time is highlighted at the left side of the figure, among EEG components at various other poststimulus windows. The violin plots show the distribution of poststimulus EEG component for standard (green) and oddball (pink) trials, respectively. On the right side of the figure, the BOLD activations specific to the 350 ms oddball EEG STV are shown inside the purple box, with BOLD activations specific to the oddball PR STV shown inside the orange box. Overlap between the spatial correlates of 350 ms oddball EEG STV and the spatial correlates of oddball PR STV are highlighted in yellow on the bottom right corner of the figure. The significant relationships between each pair of measures are represented by the dotted line between each node (i.e., pupil-EEG with line A, EEG-fMRI with line B, pupil-fMRI with line C).
components at 475 to 525 ms poststimulus time. With dual modality pupil-fMRI analysis, we also identified the spatial correlates of PDB at the ACC and frontal pole, therefore introducing the second edge and third node of the triangle (illustrated by the dotted line “C” in Figure 11.2). However, as we observed no relationship between single trial variabilities of late window EEG component and variabilities in the BOLD signal across the whole brain, the third and most critical edge of this triangle could not be found (illustrated by the grey dotted line “B” in Figure 11.2). In other words, it was not possible to identify the location at which interactions between baseline pupil-linked arousal and late window EEG component may have taken place.

Figure 11.2 illustrates the scenario when a direct combination of results from dual modality analyses do not support meaningful inferences. Once again, the top section of the figure illustrates the connection between the LC-NE system and the pupil diameter, specifically the prestimulus PDB (i.e. the first modality-specific node). On the left side of the figure, the EEG discriminating components at 475 to 525 ms poststimulus time are highlighted, and represent the second modality-specific node. Lastly, on the right side of the figure, the spatial correlates of oddball PDB STV at frontal pole and ACC are shown, and constitutes the third modality-specific node of the triple modality graph. As discussed above, while pupil-EEG and pupil-fMRI dual modality analyses yielded significant results, the lack of significant correlations between EEG and fMRI signal hindered inferences on the time and location of the interactions between pupil-linked arousal and poststimulus neural processes.

The second triple modality analysis we performed, specifically addresses this lack of correlations one may encounter when merely combining results from dual modality analyses. Although such absence of relationship between EEG and fMRI measures could be a truthful representation of the absence of interactions between tonic pupil-linked arousal and neural processes at a late window, it is equally possible that there was simply too much variance in the BOLD signal for the EEG STV-informed regressors to capture. We demonstrated that with the inclusion of additional pupillary and more importantly, pupillary and EEG interaction based regressors, we were able to better capture the variability embedded in the BOLD response. In more concrete terms, the PDB x EEG interaction predictor correlated significantly with BOLD signal in the precuneous cortex and the middle frontal gyrus. Both regions were absent from either combined pupil-fMRI or EEG-fMRI analyses.
Figure 11.2: Illustration of unidentified interactions between tonic pupil-linked arousal and neural processes around a late window (475 to 525 ms) time. The top section of the figure illustrates the connection between the LC-NE system and the pupil diameter, specifically the PDB, with standard and oddball stimulus driven pupil traces colored in green and pink, respectively. The EEG discriminating components at 475 to 525 ms poststimulus time is highlighted on the left side of the figure, among EEG components at various other poststimulus windows. The violin plots show the distribution of poststimulus EEG component for standard (green) and oddball (pink) trials, respectively. On the right side of the figure, the BOLD activations specific to the oddball PDB STV are shown inside the orange box. The significant relationships between each pair of measures are represented by the dotted line between each node (i.e., pupil-EEG with line A, and pupil-fMRI with line C). The lack of significant relationships between each pair of measures are represented by the grey dotted line between each node (i.e., EEG-fMRI with line B).
Figure 11.3 illustrates the power of this interaction term based analysis. Panel I shows that the PDB and 525 ms EEG STVs were used to create a set of interaction terms as shown in panel II. These interaction regressors were able to identify cortical regions specific to the variability of such interaction term, as illustrated in the top row of panel III. Importantly, the spatial correlates of the interaction term were largely unobserved in previous dual modality analyses (compare the regions in the yellow box to that in the orange and purple boxes). In more specific terms, the 525 ms oddball EEG STV was unable to identify any cortical regions related to the variability in neural processes at this timing, while the oddball PDB STV were correlated with BOLD response variabilities at the frontal pole and ACC, but not at the precuneus cortex and MFG. These unique findings provide further evidence on the time and location where interactions between tonic pupil-linked arousal and post behavioral response neural processes may happen. More importantly, our approach offers promising perspective on the potential of cross modality analyses, especially in investigating the spatiotemporal dynamics of systems of interest.

11.2.5 Future direction

Analyses-wise, one promising next step is to further investigate the interactions between pupil-linked arousal and EEG component STV at various poststimulus times. Given we have observed a link between ACC and middle window (425 ms) EEG variability, it will be interesting to examine if interactions between pupil and EEG variability at such window (425 ms) are correlated with the prefrontal cortex BOLD activity as well. In addition, conducting a sensitivity and specificity analysis on the interaction regressors would be useful to further justify the regressor’s capability in locating the unique cluster of activations we found.

Implication-wise, our work in this thesis may help us better understand how the arousal and reorienting systems operate in a more ecologically realistic condition. One of such conditions could be a monitoring of students’ engagement levels in a classroom or online education setting. Furthermore, our work may also contribute to the understanding of mechanisms behind mental illnesses such as obsessive compulsive disorder and depression, where the internal states of the patients are of particular interest [Benning and Ait Oumeziane, 2017, Koch et al., 2018].

In summary, our work in this thesis provides a novel spatiotemporal mapping of the dynamics, especially the dynamics of the interactions between the arousal and attention reorienting systems.
Figure 11.3: Illustration of identified interactions between tonic pupil-linked arousal and neural processes at a late window (525 ms) time. (I) With the connection between the LC-NE system and the pupil diameter, specifically the PDB, the triple modality analysis used PDB and EEG discriminating component at 525 ms poststimulus time to construct a set of interaction regressors. Standard and oddball measures are colored in green and pink, respectively. (II) The interaction regressors were used to correlate with BOLD signal, along with previously described conventional and modality-specific STV regressors (not shown). Caption continued on next page. (III) Spatial correlates of the oddball interaction regressor were identified at PCUN, MFG (shown inside the yellow box), and were largely unobserved when compared with spatial correlates of oddball PDB STV (shown inside the orange box), and the spatial correlates of oddball EEG STV at a temporally close window (600 ms, shown inside the purple box).
This is achieved by incorporating innovative approaches in both data acquisition and data analysis. Taken together, our findings provide additional evidence towards the mechanism and function of how human reorients attention to unexpected yet behaviorally relevant stimuli, and how arousal is linked to such seemingly trivial yet fundamentally critical cognitive function.
Bibliography


