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Catarina Ferreira Gomes

Age-related Changes in Arousal Modulation During perceptual Decision-making

Thesis submitted to the Faculty of Science and Technology of the University of Coimbra for the degree of Master in Biomedical Engineering with specialization in Biomedical Instrumentation, supervised by Prof. Dr. Maria Ribeiro.

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Resumo

O envelhecimento é o principal factor de risco para o desenvolvimento da maioria das doenças neurodegenerativas, tais como a doença de Alzheimer e a doença de Parkinson. A perda de neurónios noradrenérgicos do locus coeruleus (LC) é uma característica proeminente destas doenças neurodegenerativas associadas ao envelhecimento. Sendo o LC o principal núcleo responsável pela modulação do nosso estado de alerta (*arousal*), é importante explorar como este se altera com o envelhecimento, porque um sistema de *arousal* menos ativo pode ser um fator no desenvolvimento de doenças neurodegenerativas.

Para explorar esta hipótese, realizámos dois projectos, nos quais analisámos dados de adultos mais jovens e mais velhos que executaram tarefas de tomada de decisão perceptual. Num primeiro projecto, analisámos o diâmetro da pupila e o batimento cardíaco, que são medidas indirectas da actividade do LC, durante uma tarefa visual. Num segundo projecto, avaliámos tanto o diâmetro da pupila como potenciais evocados cerebrais, durante uma tarefa auditiva.

No primeiro projecto, explorámos a incerteza na resposta, que resulta na activação do sistema de *arousal*. O nosso principal objectivo era avaliar se a modulação do *arousal* pela incerteza variava com o envelhecimento. Este projecto não foi realizado até à sua conclusão, porque a pandemia de COVID-19 afetou o processo de aquisição de dados.

No segundo projecto, explorámos um potencial evocado cerebral, a positividade centro-parietal (CPP), que é um correlato neuronal do processo de acumulação de evidência observado em tarefas de tomada de decisão perceptual. Propusemo-nos a explorar o impacto do envelhecimento na taxa de acumulação de evidência neural, assim como investigar se o *arousal* tem um efeito sobre a taxa de acumulação do CPP.

Verificámos que o envelhecimento afetou a modulação da taxa de acumulação com a dificuldade de tarefa. Os adultos mais velhos apresentaram uma taxa de acumulação

mais rápida na tarefa mais fácil, enquanto os adultos jovens mostraram o contrário, uma taxa de acumulação mais rápida na condição de tarefa mais difícil. Isto indica que há diferenças nos mecanismos neuronais de tomada de decisão entre os dois grupos. Por outro lado, não encontrámos evidência de que o *arousal* tónico ou fásico sejam preditivos da taxa de acumulação do CPP.

Palavras-Chave: Electroencefalograma, Pupilograma, Envelhecimento, Tomada de Decisão Perceptual, *Arousal*, Acumulação de Evidência

Abstract

Ageing is the main risk factor for the development of most neurodegenerative diseases, such as Alzheimer disease and Parkinson disease. Loss of noradrenergic neurons in the locus coeruleus (LC) is a prominent feature of these age-related neurodegenerative diseases. Being the main nucleus in arousal modulation, it is important to explore how it changes with ageing, because a less active arousal system could be a factor in the development of neurodegenerative diseases.

To explore this hypothesis, we conducted two projects, in which we analysed data from younger and older adults who performed perceptual decision-making tasks. In a first project, we assessed pupil size and heart rate, which are indirect measures of the activity of the noradrenergic LC, during a visual task. In a second project, we assessed both pupil size and event-related potentials during an auditory task.

In the first project, we explored response uncertainty, which results in the activation of the arousal system. Our main goal was to assess whether the modulation of arousal by uncertainty varied with ageing. This project was not conducted until its completion, because the COVID-19 pandemic affected the data acquisition process.

In the second project, we explored an event-related potential, the centro-parietal positivity (CPP), which is a neural correlate of the evidence accumulation process observed in perceptual decision-making tasks. We set out to explore the impact of ageing on the rate of neural evidence accumulation, as well as whether pupil-linked arousal and task performance have an effect on this CPP build-up rate.

We found that ageing affected the modulation of the build-up rate with task difficulty. Older adults presented a faster build-up rate while engaged in the easier task condition, while young adults showed the opposite, a faster build-up rate in the more difficult task condition. This indicates that there are differences in the decision-making neural mechanisms between groups. On the other hand, we did not find tonic or phasic arousal to be predictive of the CPP build-up rate.

Keywords: Electroencephalogram, Pupillogram, Ageing, Perceptual Decision-making, Arousal, Evidence Accumulation

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Acronyms

2AFC Two-Alternative Forced Choice

ACC Anterior Cingulate Cortex

ANOVA Analysis of Variance

ANS Autonomic Nervous System

CG Ciliary Ganglion

CNV Contigent Negative Variation

CNS Central Nervous System

CPP Centro-Parietal Positivity

DDM Drift Diffusion Model

ECG Electrocardiogram

ECM Eigenvector Centrality Mapping

EEG Electroencephalogram

ERP Event Related Potential

EW Edinger-Westphal

fMRI Functional Magnetic Resonance Imaging

GLM Generalized Linear Model

HR Heart Rate

HRV Heart Rate Variability

IBI Interbeat Interval

IC Inferior Colliculus

ICA Independent Component Analysis

ITPC Inter-Trial Phase Coherence

LBA Linear Ballistic Accumulator

LC Locus Coeruleus

MCN Mesencephalic Cuneiform Nucleus

MFC Medial Frontal Cortex

mPFC Medial Prefrontal Cortex

NE Norepinephrine

NM Neuromelanin

PCC Posterior Cingulate Cortex

PEP Pre-Ejection Period

PES Post-Error Slowing

PGi Paragigantocellularis

PLR Pupillary Light Reflex

PON Pretectal Olivary Nucleus

PSNS Parasympathetic Nervous System

RDK Random Dot Kinematogram

RZI RZ Interval

RT Reaction Time

SAT Speed-Accuracy Trade-off

SBCA Seed-based Functional Connectivity Analysis

SC Superior Colliculus

SCi Intermediate layer of Superior Colliculus

SCs Superficial layer of Superior Colliculus

SDT Signal Detection Theory

SNS Sympathetic Nervous System

vmPFC Ventromedial Prefrontal Cortex

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Introduction

1.1 Motivation

Having good decision-making skills as an older adult is crucial for maintaining physical and mental well-being. It is important to study the neural mechanisms that underlie deficits in decision making in older adults because this makes it possible to propose efficient strategies that help overcome these problems and that will affect the performance of everyday tasks.

Besides, ageing is the main risk factor for the development of most neurodegenerative diseases, such as Alzheimer disease and Parkinson disease [1]. The number of older adults in society has been increasing, and therefore it is important to study the mechanisms that underlie the effects of age in these diseases. To understand this, researchers need to start by finding out which changes in cognition are normal to occur with ageing and which changes may suggest a brain disease. Studying the relationship between the brain, its arousal systems and ageing in healthy individuals might help to understand what could possibly cause the onset of the neurodegenerative diseases that are associated with ageing. Particularly, by assessing whether the arousal system is affected by ageing, we can test the hypothesis that a less active arousal system is a factor in the development of neurodegenerative diseases.

To achieve this goal, we started a project called *"Processing of Decision Uncertainty in Older Adults: Assessing Behaviour, Pupil Size and Heart Rate"*. This project lies on the fact that when we are uncertain about a decision, there is an activation of the arousal system. We wanted to know whether this uncertainty processing was different between younger and older adults, and whether this arousal activation was modulated by uncertainty in older adults. Therefore, we designed a perceptual decision-making experiment, in which we would acquire data from younger and older adults, and assess how the response of the arousal system changed with ageing, by studying two measures of arousal: the pupil size and the heart rate. Due to

the ongoing global pandemic of COVID-19, and considering that this first project required acquiring data from older subjects, who are at higher risk of severe illness from COVID-19, I personally did not feel like it was safe to move forward with this project. However, I was able to acquire and analyse some preliminary data, which made me familiarized with the technical skills involved in these types of experiments. Besides, this project allowed me to explore the concepts of arousal, cognitive processing, ageing of the brain, among others, which are of great relevance to the project that I then conducted.

This second project, entitled *"ERP Markers of Evidence Accumulation during Perceptual Decision-making, their Modulation by Arousal, and Age-related Changes"*, explores the role of the arousal systems in the evidence accumulation process during perceptual decision-making, with the main goal of assessing whether arousal modulates the speed of evidence accumulation and if this modulation changes with ageing.

The next few sections present an overview of concepts and mechanisms relevant to both projects, such as the effect of ageing on cognitive processing, the role of the autonomic nervous system (ANS), and the effect of ageing on ANS responses.

1.2 Effect of Ageing on Cognitive Processing

Cognitive functioning refers to the several mental processes that help us to understand and support behaviour. It is essential to have these skills because they allow us to carry out simple and complex tasks and ultimately live independently and as a society. This includes cognitive functions that are divided into several domains, such as memory, attention, perception, executive cognitive function, language, decision making, among others. There are, however, factors that lead to a decline of cognitive functions, particularly with ageing, and this can result in losing the ability to perform a range of daily tasks.

It is well known that cognitive abilities decline with age and it is crucial to study the mechanisms that underlie the effect of age on cognition because the number of older adults in society has been increasing and consequently, cognitive decline tends to have a stronger impact [2]. To further understand this, it is important to know which changes in cognition are normal to occur with ageing and which changes may suggest a brain disease.

Regarding most of the cognitive domains, three stages have to occur: perception of the stimulus, processing of the information and response. With ageing, the reduced

sensory perception and the slowdown of processing speed may result in a poorer performance in several cognitive domains [2].

Attention and memory are the basic cognitive domains that are most negatively affected by ageing [3]. Perception, even though considered by most people to occur prior to cognition, can have a significative impact on cognition. This domain has also been reported to present age-related declines, which are mainly due to declining sensory abilities, such as hearing and vision loss [3].

Complex cognitive functions, such as language and decision making, are highly dependent on the basic cognitive functions, such as memory, attention and perception, and therefore their integrity is influenced by the state of those basic cognitive functions. Overall, language tends to resist brain ageing and it can even improve with age [2, 3, 4]. Concerning decision making, not much research has been done directly on the effect of age on decision making, but rather on the impact of attention and memory declines on decision making. Besides, most studies examined the impact of prior knowledge, emotion and relevance on decision making. For example, it has been shown that older adults rely more on prior knowledge and less on new information, whereas young people, which are likely to know less about the issue being concerned, tend to consider more current information and to study more alternatives before making a decision [3].

These complex cognitive tasks are also thought to depend on executive functions. Executive functioning involves processes such as planning, organization, mental flexibility and problem solving. Evidence points to deficits in executive functions as major contributors to the age-related cognitive decline [2, 3, 4].

Another age-related phenomenon in cognitive tasks is the speed-accuracy trade-off (SAT) typically found in older adults. Even though ageing is associated with worse cognitive control and that, in turn, is associated with increased number of errors, older adults seem to be able to avoid errors by trading off speed for accuracy. It has even been found that this leads to older adults being more accurate than younger adults [5]. There is, however, more than one explanation possible to justify the fact that older adults take more time to react. The first reason could be that older adults are more cautious and afraid to make mistakes. For that reason, in order to avoid them and to have a very good performance, they voluntarily become slower so that they are more likely to react in a correct manner. The second reason is that with age there is an increase in neural deficiencies that result in the slowdown of mechanisms associated with task performance. This reason is correlated with the striatal hypothesis of the SAT [6], which proposes that speed stress leads to

an increase in the input from cortex to striatum. Consequently, activation of the striatum disinhibits the cortex and allows faster responses. This hypothesis would therefore explain the speed-accuracy trade-off found in older adults: this slowing might not be a strategic choice but rather a result of the degeneration of the white matter connections in the elderly. In order to study these hypotheses, Forstmann et al. (2011) [6] investigated the SAT and how it is implemented in the brain, by using a decision-making task that instructed young and old subjects to respond quickly or accurately. The results were consistent with the striatal hypothesis as they showed relatively weaker white matter connections in the older group. Overall, this suggests that older adults are cautious not just because of their own worries and preferences, but partially because of their brain limitations.

Taken together, most studies that investigated the effect of ageing point to a cognitive decline. However, there is a lot of variability across people and, in some cognitive tasks, older adults can even perform better than younger adults [3]. While some cognitive functions, such as language, can even improve with age, others, such as memory and processing speed, are likely to decline with ageing.

1.2.1 Brain Structural Changes in Ageing

Research shows that these age-related changes in cognitive function are due to alterations in brain structure and function. In fact, the volume of the brain decreases with age and gray and white matter regions are significantly affected [2].

Gray matter volume decline is most noticeable in the prefrontal cortex, while changes in temporal lobes are more restrained, involving decreases particularly in the medial temporal lobe, which includes the hippocampus [2, 4]. White matter volume also declines with age, with the biggest declines being reported to occur in the frontal lobe and in areas such as the corpus callosum. Apart from the decreases in volume, declines in white matter integrity have also been reported [2, 4].

The loss of neurons itself has been thought of as a likely cause to the gray matter volume loss. However, gray matter volume loss is best explained by the structural changes that occur with age, such as the decrease in number and length of dendrites, decrease in the number of axons, increase in axons with segmental demyelination and a substantial reduction of synapses [2].

In addition to the decline in cortical and hippocampal regions that occurs with ageing, brainstem regions also play a role in determining age-related cognitive changes, particularly the locus coeruleus-norepinephrine (LC-NE) system. The LC is a small

nucleus in the pons of the brainstem that is the main source of NE synthesis. The LC-NE system is a part of several mechanisms, such as modulation of attention, arousal and cognition, as well as sleep/wake states, memory and stress responses. Neurons in the LC-NE system have two firing modes: tonic and phasic. In the phasic mode, NE neurons fire at a low baseline rate but have bursts of action potentials in response to salient stimuli. The tonic mode is associated with a higher baseline firing activity and no phasic responses. The phasic mode is activated in response to relevant stimulus, but not in response to distractors, therefore it seems to optimize performance and attention during a task [7, 8, 9]. On the other hand, the tonic mode is more efficient in sustained processing and is associated with a high baseline firing rate in the LC, promoting detachment from the task. Therefore, this mode is associated with poor performance on tasks that require focused attention and corresponds to apparent increases in distractibility [9]. Even though the tonic mode results in worst performance, it promotes the switch from the current task to the processing of stimuli or actions that are not related to that task [7, 10]. In other words, it increases flexibility, favoring exploration [8, 9]. These results led to the Adaptive Gain Theory, which suggests that the LC-NE system has a very important role in controlling performance. In fact, there is an inverted U-shaped relationship between performance and tonic LC-NE levels [11]. This theory further proposes that this plastic LC phasic response is driven by the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) [7, 9]. Being the main nucleus in arousal modulation, it is important to explore how it changes with ageing, because it could play a factor in the onset of neurodegenerative diseases. For instance, a major feature of Alzheimer's disease is the loss of noradrenergic LC projection neurons [12].

Age-related cell loss in the LC has been reported, however, there is no clear evidence about this LC decrease in neuron counts, as some studies did not find age differences [13]. Despite uncertainty regarding this change, there is evidence that LC integrity is associated with cognitive abilities in older adults. Wilson et al. (2013) [14] examined the density of neurons in several brain regions, including the LC, the dorsal raphe nucleus, the substantia nigra and the ventral tegmental area, in the autopsy of older adults that completed on average 6 years of cognitive testing before dying. When modeled together, only LC neuronal density was related to the cognitive decline that was shown in the years before death.

MRI neuromelanin (NM) imaging has also been reported to operate as an indirect measure of LC integrity. With age, NM accumulates in the LC and plays a neuroprotective role [13]. Hämmerer et al. (2018) [15] tested the hypothesis that the LC integrity varies with age and is likely to cause altered cognitive performance in older

adults. In order to study this, young and older adults performed a reversal learning task while acquiring MRI data. The results showed that the older adults that had diminished LC integrity, i.e. lower mean NM signal intensity, showed poorer memory performance. This supported the idea that LC integrity is associated with the age-related decline in cognitive functioning.

1.2.2 Cardiac Changes in Ageing and their relationship with Brain Function

The changes in the brain that occur with ageing are also known to interact with other organs, such as the heart. Specifically, heart rate variability (HRV) is a non-invasive measure of the ANS, which is known to decrease with age and is associated with cognitive functioning [16]. Modulation of the heart rate arises from the parasympathetic influences on the heart. The Neurovisceral Integration Model considers the role of the brain in parasympathetic cardioregulation and proposes that frontal and midbrain areas interact and the prefrontal cortex inhibits subcortical regions as well as the ANS [17]. Therefore, the heart is under tonic inhibitory control by the ANS, via the vagus nerve. Given this close interaction of the brain and the ANS in heart rate regulation, several brain regions have been reported to relate to HRV. These brain structures are the medial prefrontal cortex (mPFC), the ACC and the posterior cingulate cortex (PCC).

Kumral et al. (2019) [17] investigated the association of resting HRV with brain structures and functional connectivity in younger, middle-aged and older healthy adults, using resting-state functional magnetic resonance imaging (fMRI) and electrocardiogram (ECG). They used a large sample of 388 healthy adults and using Eigenvector Centrality Mapping (ECM) and Exploratory Seed-based Functional Connectivity Analysis (SBCA), they showed that the PCC correlated with resting HRV in all age groups, and the ventromedial prefrontal cortex (vmPFC) correlated with resting HRV in young but not in the middle-aged or the older group. These findings support the idea that the age-related decrease in HRV is due to changes in functional connectivity along the cortical midline.

1.3 The Role of the Autonomic Nervous System

The ANS is comprised of the efferent neurons that innervate smooth muscle, cardiac muscle and glands. Thus, it plays a role in the maintenance of homeostasis. The ANS regulates these areas autonomously, i.e., its functions are not under our conscious

control.

The ANS has two functional divisions: the sympathetic (SNS) and the parasympathetic (PSNS) nervous systems. The SNS is associated with the fight-or-flight response, while the PSNS is associated with the rest and digest response. The SNS regulates several body processes in response to threat and stress, performing tasks such as dilating eye pupils, speeding up heart rate and relaxing the bladder. The PSNS helps to conserve resources and maintain basic body functions, such as digestion, urination and salivation. There are also Central Nervous System (CNS) components of the ANS, including the brainstem and spinal autonomic preganglionic neurons that project to the autonomic motor neurons in the peripheral ganglia.

Both divisions of the ANS are tonically active, meaning that they send input to certain tissues at all times and, consequently, the activity of the tissue may be increased or inhibited [18]. The natural opposition in the function of both systems is better described as complementary. Increasing the activity of one system while decreasing the activity of the other one leads to a quick and precise control of the activity of the tissue.

The activity of the ANS has been reported to vary with brain arousal [19]. Brain arousal is associated with the human behaviour, including how we respond to external stimulation and to events such as thoughts, noises, emotions and effort [20]. For example, arousal is increased when facing threat and decreased during rest.

1.3.1 Influence of the Autonomic Nervous System on Pupil Responses

The diameter of the pupil is a non-invasive measure of autonomic activation. The ANS influences several ocular functions, one of them being the pupil diameter. The pupil is the aperture situated in the center of the iris of the eye that allows light to pass through the surface of the lens and reach the retina in the back of the eye, which as a result, allows vision [21].

The size of the pupil is determined by two sets of muscles in the iris: the sphincter muscles, which decrease its size and the dilator muscles, which increase it [22, 23]. These processes are controlled by the balanced activity between the sympathetic system and the parasympathetic system [22, 24, 25].

In the sympathetic system, which promotes dilation (mydriasis), pre-ganglionic fibers project from the hypothalamus to the superior cervical ganglion (SCG), via

the spinal cord, and post-ganglionic fibers project to the iris dilator muscles, via ciliary nerves [25, 26].

In the parasympathetic system, which promotes constriction (miosis), retinal ganglion cells project to the pretectal olivary nucleus (PON), which then projects to the Edinger-Westphal (EW) nucleus. Finally, neurons in the EW project to the ciliary ganglion (CG) to regulate the sphincter muscles of the iris [25]. The influence of these two nervous systems is visually represented in Figure 1.1.

Pupil size is sensitive to a variety of factors, including light. The pupillary light reflex (PLR) is the transient constriction in pupil diameter that happens as a result of an increase in light flux. Similarly, when luminance decreases, the pupil size increases. The PLR results from a circuit that involves the retina, the EW nucleus and the pupillary sphincter muscles. However, its magnitude does not depend exclusively on retinal input. In fact, it has been found that microstimulation of the frontal eye field also modulates this reflex, suggesting that attention might modulate this reflex [27].

Another factor that can alter pupil size is cognitive load. Particularly, pupils dilate with increasing cognitive workload and with increasing task demands. In other words, the amplitude of the pupil dilation is higher when performing a more complex task than when performing a simpler task. Therefore, pupil dilation gives indirect access to cognitive processes, such as decision-making, memory, attention and vigilance. Task demands usually generate pupil dilation in the three domains of executive control: switching, updating, and inhibition [22]. However, the mechanism underlying this correlation is not clear. Two interpretations are possible, one suggests that pupil dilation simply reflects the task demands, while the other is more complex, suggesting that pupil dilation actually reflects the effort employed in response to the demands [22]. In order to understand if pupil dilation is an index of effort, Van der Wel et al. (2018) [22] reviewed numerous studies concerning pupil dilation and its link with cognitive tasks. Taken together, the preliminary results favor the idea that pupil dilation is an index of the exerted effort and not just a mere reflection of the task demands. Furthermore, in some situations, pupil dilation in response to cognitive tasks was shown to predict improved task performance [22]. Indeed, in some studies, individuals with increased pupil dilation showed better task performance than individuals with smaller pupil dilation.

Emotional arousal is another important factor in the modulation of the pupil's response. It has been demonstrated that emotionally arousing stimuli, such as affective picture viewing or auditory emotional stimulation, trigger an increase in pupil size,

more than emotionally neutral stimuli [21, 28, 29].

Fatigue is also responsible for changes in pupil size. It has been found that increases in mental fatigue are linked to diminished stimulus-evoked pupil dilation [30]. This is particularly important when conducting pupil-related tasks because fatigue may be increased by mental demands and may result in a decrease in performance. Therefore, as well as maintaining the luminance constant, it is crucial to avoid fatigue by imposing work-pause regimes when studying pupil responses.

The balance between the sympathetic and the parasympathetic nervous system, which regulates pupil size, is controlled by other circuits that give rise to pupil changes in response to changes in these properties, such as light and cognition.

There has been growing evidence of the brain mechanisms that are in the basis of effort-related pupil dilation. In fact, it is known that the LC-NE system is tightly linked with the modulations in arousal that activate pupil response in response to cognitive load. Joshi et al. (2016) [31] found relationships between neural activity and pupil diameter in several brain structures: LC, intermediate layer of superior colliculus (SCi), ACC, PCC and inferior colliculus (IC).

The relationship between LC activity and pupil diameter has been reported to depend on a common input to the LC and the EW nucleus: the paragigantocellularis nucleus of the ventral medulla (PGi) [22, 31, 32]. The PGi receives inputs and projects to the EW nucleus, which controls pupil constriction, and to the LC [31].

In addition to this, there is another pathway that can influence pupil diameter. This circuit involves the superior colliculus (SC) [25, 31, 32], which is separated into intermediate layers (SCi) and superficial visual-only layers (SCs) [25]. The SCi receives inputs from the SCs, frontal-parietal areas, the basal ganglia (BG) and the LC [25, 26]. The SCi projects directly and indirectly, via the mesencephalic cuneiform nucleus (MCN), to the EW, and can therefore activate or inhibit the parasympathetic pathway [25]. These pathways are represented in Figure 1.1.

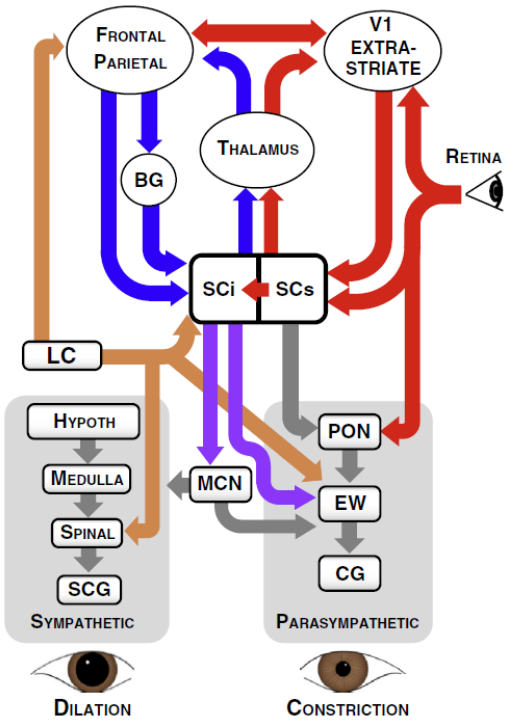


Figure 1.1: Pupil orienting circuit. Abbreviations: BG, basal ganglia; CG, ciliary ganglion; EW, Edinger-Westphal nucleus; Hypoth, hypothalamus; LC, locus coeruleus; MCN, mesencephalic cuneiform nucleus; PON, pretectal olivary nucleus; SCi, intermediate layers of the superior colliculus; SCs, superficial layers of the superior colliculus; SCG, superior cervical ganglion; V1, primary visual cortex. Reprinted from [25].

Joshi et al. (2016) [31] also found that fluctuations in the LC activity, related to pupillary responses, consistently occurred before those in SCi and in IC. This may mean that NE release contributed to neural alterations in these other brain structures. However, such contributions could also involve other neuronal pathways. For example, the ACC sends and receives projections to and from the LC, and the ACC is strongly connected with the PCC. These other circuits can explain the timing variability described between the cingulate cortex, LC, IC and SCi.

In a similar way to the NE synthesized in the LC, it has been proposed that acetylcholine has an important role in compensatory mechanisms to maintain task performance when in challenging conditions. In fact, acetylcholine neurons have been demonstrated to upregulate pre-frontal areas in response to cognitive tasks and they also receive input from frontal and midbrain areas, therefore being in an ideal location to regulate motivated behaviour. Importantly, Reimer et al. (2016) [33] has shown that the activity in cholinergic and noradrenergic axons in the neocortex is reflected by pupil dilation: persisting dilations of the pupil are associated with

cholinergic activity, while rapid dilations are accompanied by noradrenergic activity.

Overall, we can conclude that measuring changes in pupil diameter is an indirect way of inferring activity fluctuations in the LC. In other words, pupil diameter is a reliable index of activity in neuromodulatory arousal systems, including the LC, and this is why we measured and analysed pupil size in both of our projects.

1.3.2 Influence of the Autonomic Nervous System on Heart Responses

As mentioned, the ANS is vital for several subsystems, the cardiovascular being one of the most examined, given the easiness of measuring its biosignals, such as the heart rate. The heart rate is a constantly changing parameter and studying this HRV is a way of getting more information about the cardiovascular modulation by the ANS.

HRV is the variation in the time interval between each heartbeat (R-R interval), given in milliseconds. This variability is originated by the ANS, resulting from a variability in balance between the activity of the sympathetic and the parasympathetic (vagus) nerves, at the sinoatrial node.

Both divisions of the ANS are tonically active, with sympathetic activity responsible for heart rate acceleration and parasympathetic activity related with heart rate deceleration.

HRV is also on the basis of the relationship between ANS and cognitive functioning. This relationship is not extensively understood but autonomic changes have been reported to occur simultaneously to cognitive functions, such as arousal, attentional orienting and alerting [16].

The Neurovisceral Integration Model, proposed by Thayer et al. (2009) [18], is the most known theory to describe this relationship, indicating that there is a cortical network linking cognitive, emotional and autonomic regulation to HRV and cognitive performance. This network is comprised of the prefrontal cortex, the anterior cingulate cortex, the insula, the amygdala and the brainstem. According to this model, a sympathetic hyperactivation, with consequent prefrontal hypoactivation, leads to the disinhibition of the amygdala, which in turn causes a decrease in HRV and an increase in heart rate. This path is associated with declined cognitive functioning. On the other hand, lack of prefrontal hypoactivation is associated with an increase in HRV and a reduction in heart rate, with enhanced cognitive functions [16]. These

pathways by which prefrontal cortex might influence heart rate are represented in Figure 1.2.

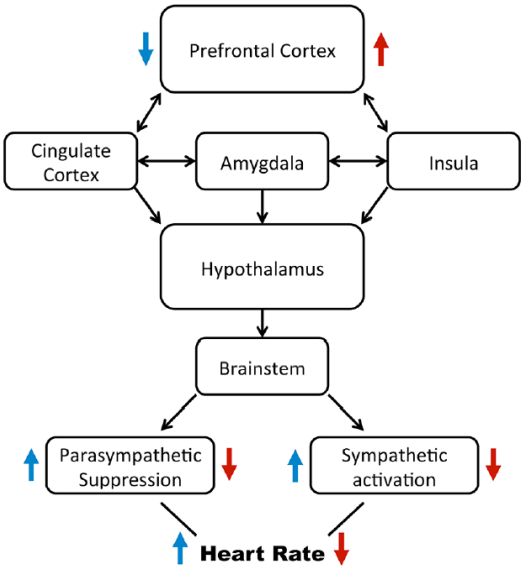


Figure 1.2: Representation of the Neurovisceral Integration Model described by Thayer and Sternberg. Reprinted from [34].

Indeed, several studies have found an association between increased resting HRV and improved cognitive functioning, in particular with respect to enhanced behaviour (e.g., better accuracy and faster response times) on tasks that required executive functions, such as the Stroop task [35]. On the other hand, when resting HRV levels were diminished, studies found that performance on executive tasks declined, with people failing to identify safety cues and to adjust to novel and neutral stimuli [36]. Furthermore, when resting HRV levels were lower, subjects tended to respond to neutral stimulus with increased neural responses, as if they were actually emotionally negative stimulus [36]. This clearly means that there is an association between HRV and the prefrontal circuits, for cognitive and emotional regulation, as proposed by the Neurovisceral Integration Model.

Tasks that induce a state of attentiveness and alertness are associated with a heart rate deceleration prior to the reaction stimulus [37, 38, 39, 40, 41]. This cardiac deceleration is under vagal control and is thought to help prepare for the subsequent response, speeding up reaction times and enhancing decision-making. In these reaction time task studies, a biphasic heart rate response has consistently been reported: deceleration in anticipation of the stimulus and acceleration following response onset.

Another finding that has consistently been observed is that this cardiac deceleration is associated with reaction time, in decision-making tasks. Indeed, heart rate deceleration was increased when subjects were required to respond fast compared to when they were allowed to respond slower [38]. Furthermore, preparatory heart rate deceleration seems to correlate positively with reaction time [41].

The complexity of the task has also been found to correlate with cardiac deceleration. In fact, increasing the number of possible responses leads to an increased task complexity which results in an increased anticipatory cardiac deceleration [37]. This modulation of cardiac deceleration with task complexity is associated with an ability to maintain response speed as complexity increases, because the cardiac deceleration is thought to facilitate decision-making.

1.4 Effect of Ageing on ANS Responses

The activity of the ANS varies with brain arousal. Therefore, to study the effect of ageing on arousal, it is important to study what changes in the ANS responses with ageing, for instance in pupillary responses and in HRV.

The studies that elaborated on the effect of ageing on task-related pupillary responses tend to find inconsistent results. As an example, Van Gerven et al. (2004) [42] investigated age-related pupillary responses to a memory-search task and the results showed no age differences during the encoding phase of the experiment. However, in the search phase, pupil dilation was significantly larger in the young than in the older group. Hämmerer et al. (2017) [29] investigated age differences in response to negative emotional images and found that older adults showed diminished pupil dilation to the negative stimuli. In another study related to emotion, Tianyuan Li et al. (2010) [43] recorded two layers of the emotion regulation process: attention (measured by percent fixation duration) and cognitive effort (measured by pupil dilation) toward a positive and a negative image. The results showed that older adults had a lower percent fixation duration than young adults, but they did not present differential pupil dilation when looking at the negative image, that is, pupillary responses showed no age-related differences. Similarly, Ribeiro et al. (2019) [44] did not find a significant effect of age in the amplitude of task-related pupillary responses, during a cued reaction time task. However, by investigating different parameters associated with pupil responses, the authors managed to find age-related differences. Indeed, the time derivative of pupil responses in response-locked measurements presented significantly more negative values in the older group compared

to the younger group. Furthermore, by studying the latency of the pupil dilation peak, it was found that this interval was substantially reduced in the older adults. The amplitude of this peak was also examined, but no significant age differences were found. Overall, these results indicate that the dynamics of pupillary responses change with ageing.

The variability in results is probably due to a series of methodological differences across studies. These differences can be related to the cue-target time interval, the task demands (detection vs. discrimination), the saliency of the alerting cue, among others. Besides, the pupil diameter of older adults is generally smaller than that of younger adults and therefore they have a more limited range of pupil dilation [45], so it is important to correctly account and control for this factor during data analysis. Overall, the results of previous studies indicate that age-related changes in pupil diameter may be dependent on the type of task and task demands.

In addition to pupil responses, it is known that the ANS is indexed by the HRV. A low HRV is associated with impairments in cognitive function and the HRV is known to decline with age. The two divisions of the ANS that play a role in the origin of HRV change differently with age, because they have different neural origins. It is thought that ageing causes a decline of the parasympathetic activity in the sinoatrial node, which has been reported to be related with the consistently observed cognitive impairment [46]. This age-related decline in the parasympathetic function causes an increased risk of cardiovascular diseases, such as arrhythmia and sudden cardiac death [46].

As mentioned, most previous studies have found a constant decrease of HRV to occur with ageing, in large samples of subjects. For example, Zhang et al. (2007) [47] collected data from 470 healthy subjects and showed that the overall autonomic activity, measured by baseline HRV, consistently decreased from the age groups 10+ to 80+ years. Besides, low frequency (represents some sympathetic activity) and high frequency (represents some parasympathetic activity) declined as age increased. Similarly, Bonnemeir et al. (2003) [48] collected data from 166 healthy volunteers and demonstrated that HRV decreased with age. In contrast, Tan et al. (2019) [46] investigated if reductions in HRV reflecting cardiac vagal tone are linked to ageing, in a sample of 45 healthy subjects. Contrary to the results previously presented, this study did not find any age-related HRV changes.

The relationship between age and cardiac responses in decision-making tasks has not been extensively studied. Ribeiro et al. (2019) [37] addressed this relationship using a cued task, with two conditions: a simple reaction time condition and a go/no-

go condition. In addition to these conditions, a percentage of cue-only trials was introduced, in which a cue stimulus was presented but no go stimulus was followed, meaning that no response was required. In these cue-only trials, the younger adults showed a larger cardiac deceleration amplitude in the go/no-go task, unlike the older subjects, who did not modulate their heart deceleration with the type of task. This suggests that older adults present weaker cardiac responses and impaired modulation of the heart rate with task demands. Similarly, regarding the cardiac acceleration that tends to follow the deceleration response, the younger adults presented larger cardiac accelerations than the older adults, supporting the idea that heart rate recovery is affected with ageing. However, ageing did not show an effect with regard to the heart rate acceleration that is associated with the execution of the motor response, i.e., the button press. Finally, and in line with what was expected, baseline heart rate was diminished in older adults.

In the same study [37], as task complexity increased, older adults presented a slow-down of reaction times, more so than the younger group. Therefore, this supports the fact that ageing negatively impacts the modulation of cardiac deceleration with task demands, resulting in worse task performance, given by longer reaction times. Furthermore, in the same group of participants, cardiac deceleration did not correlate with reaction time, once again in contrast to what was observed in younger adults.

2

Processing of Decision Uncertainty in Older Adults: Assessing Behaviour, Pupil Size and Heart Rate

2.1 Project Aims

This study arises from the fact that when we are uncertain about a perceptual decision, there is an activation of the arousal system. One aim of this project is to assess the hypothesis that the processing of uncertainty is different in younger and older adults. Previous studies have shown that in younger people, the more uncertain the person is at response onset, the more their arousal system is activated, and this is evident in their pupil diameter. Therefore, we intend to find out if this modulation of the arousal activation by uncertainty is also present in older adults. Another aim is to observe how this processing of uncertainty affects how people react to positive or negative feedback, later on in the decision-making process. Being that ageing is the primary risk factor of neurodegenerative diseases, our overall goal is to assess if the arousal system is affected by ageing, to understand if a less active arousal system could be a factor in the development of neurodegenerative diseases, such as Alzheimer's disease.

As previously mentioned, both the pupil size and the heart rate are indicators of the arousal state. It has been shown that errors during a decision-making process evoke ANS responses, eliciting an increase in pupil diameter and a decrease in heart rate. In addition to this, these responses are increased in consciously perceived errors compared to unreported errors [49]. In older adults, error awareness is diminished [50], and there is a possibility that this could be related to the age-associated reduc-

tion of ANS activity. Error awareness is crucial because it can lead to the adoption of compensatory mechanisms and, as a result, performance optimization.

Uncertainty during a decision-making process is a part of the same cognitive process as error awareness. For instance, when a subject thinks their response is incorrect, they are uncertain of their response, and vice versa. This uncertainty is another important variable because not only it influences the current decision being made, but it also seems to guide subsequent choices and drive changes in pupil-linked arousal state [51]. The more specific aims of this study are to assess if: 1) the post-decision pupil dilation related to decision uncertainty will be reduced in older adults, 2) the post-decision heart rate deceleration is increased when the subject is more uncertain of their response and how does this response vary with age. We also want to investigate if there is a relationship between response certainty and feedback processing. For instance, if a subject is uncertain of their response and the feedback comes back as negative, their pupil response might be smaller than when the subject is confident that they got the response correct but feedback is also negative. This can indicate if older adults tend to think that they got a response correct despite it being wrong.

To assess these hypotheses, and if there had been the possibility to take up this project until its completion, pupil responses and heart rate would be measured while subjects performed a two-alternative forced choice (2AFC) task, with varying difficulty.

2.2 The Importance of Error Monitoring

A very important process in everyday life is monitoring our performance, particularly our errors. Alongside monitoring, it is useful to use the information given to us by these errors to adjust our behaviour and prevent similar errors. In order to do this, it is crucial that we are aware of the errors we make. However, it is known that error awareness declines with normal ageing [50].

Making errors during a decision-making task is clearly associated with an increased response of the ANS. Indeed, both increased pupil diameter [52, 53, 54, 55, 56] and decreased heart rate [57, 58, 59, 60, 61, 62] have been shown to occur after erroneous responses. Besides, these responses present higher amplitude for reported than unperceived errors [49]. When a subject is aware of their own error, it is likely that their decision confidence is low and vice-versa. Therefore, these findings suggest that confidence in a decision modulates the ANS response. In the same manner, if

a subject is very certain that they made an error, then an error can be associated with a high degree of certainty.

The brain structures that originate the processes that are responsible for performance monitoring, error detection and behaviour adjustment have also been located. These are the posterior medial and lateral parts of the frontal cortex as well as the insular cortex [53, 63, 64]. The dorsal ACC, which is a structure located in the medial frontal cortex (MFC), sends and receives projections to and from the LC. Besides, activity in the ACC has been shown to predict error-related pupil dilation [65]. Therefore, it could be hypothesized that the MFC monitors performance and when in need of cognitive resources, it signals to the LC, which in turn modulates processing in the cortical areas that are associated with task performance [7, 65]. Indeed, the noradrenergic neurons of the LC project into all parts of the brain.

A very important event frequently found after errors is post-error slowing (PES). This is considered to be a type of behavioural adjustment and refers to the slowing that usually happens after errors and that results in longer reaction times following error trials compared to following correct trials [66]. PES has been found in several types of tasks that are associated with the inhibition component of cognitive control [67], but there have been studies in which no effects of PES were observed.

It has been suggested that there is a correlation between PES and error awareness, however findings are not consistent. Most studies found that PES was larger following perceived errors than unnoticed errors, but others did not observe any PES effect and some even found a PES effect after unperceived errors [66, 67]. Therefore, further studies are needed to assess this correlation, ideally using a larger variety of tasks.

An association between age and PES has also been studied. As an example, Wessel et al. (2018) [56] used an eye movement task and predicted, based on other authors' studies, that older adults would show increased PES. Furthermore, Wessel et al. (2018) [56] assessed the correlation between the age-related increase in PES and error awareness, particularly in regard to consciously reported and unreported errors. The resultant data from this study showed that PES effect was observed but it did not show differences between unreported and reported errors. In addition to that, there was some evidence that pointed to an increased PES in older adults compared to younger adults, however this effect was limited to reported errors. The fact that the slowing effect was solely associated with reported errors can be risky, since older adults present error awareness impairments.

This ability to detect errors and to adjust behaviour is elevated in young healthy adults but shows some deficits in the older population as well as in several clinical conditions, as demonstrated in several studies. James et al. (2011) [68] examined how younger and older adults performed in a task in which they had to find experimenter-introduced errors. As expected, young adults found more errors than older adults. Harty et al. (2013) [69] assessed age-related error awareness using a variant of the go/no-go error awareness task and found that older adults exhibited substantially poorer awareness compared with young adults, despite the fact that the two groups were matched for overall accuracy. Niessen et al. (2017) [5] evaluated the performance of participants aged between 20 and 72 years old in an adapted version of the go/no-go task and demonstrated that higher age was associated with a greater proportion of undetected errors. Masina et al. (2018) [66] found similar results, in an experiment that revealed a main effect of group: younger adults were more aware on their commission errors than children and older adults.

Given that in younger adults, error commission and error detection are accompanied by phasic autonomic arousal [63], led to the hypothesis that the error awareness deficit in older adults is caused by the declining autonomic reactivity and reduced phasic arousal that is associated with ageing [70]. To test this, Wessel et al. (2018) [56] measured pupil diameter in younger and older adults during an eye movement task. As predicted, older adults were less aware of errors. In addition to that, younger adults, but not older adults, showed some evidence of error awareness on unreported errors. Older adults showed no pupil dilation to unreported errors, in agreement with this lack of error awareness in those trials. Besides, they showed a diminished pupil response to reported errors. Overall, these results suggest that diminished autonomic reactivity can be a cause or a consequence of age-related error awareness deficits.

The fact that error awareness is impaired in the elderly, comes with several concerns and challenges. The ability to detect errors and to monitor performance is essential to adopt behavioural adjustments and compensatory mechanism. Being that this ability is reduced in older adults, it can mean that problems associated with their declining sensorimotor mechanisms will be aggravated. Examples of this include participating in risky behaviour, increased caregiver burden, poor motivation for treatment and poor general prognosis [50, 56, 69].

In addition to PES, which is considered to be a long-term adjustment, there is another post-error action that has been reported to occur after an error: immediate corrective behaviour. Two interpretations have been reported, the first one suggest-

ing that PES is originated as an adaptive cognitive control increase, which makes people more cautious after an error, therefore taking longer to respond in the next trial. The second theory attributes PES to an orienting mechanism, suggesting that attention is shifted toward the error because these are usually rare occurrences. Consequently, this orientation to the error as opposed to orientation toward the task, causes a slower response in the following trials. Another alternative, which is in line with the first interpretation concerning the cognitive control of PES, is that PES is associated with an increase in effort.

In order to investigate the mechanism responsible for PES, Spruit et al. (2018) [71] used flanker and switch tasks, while recording two different cardiac measures. The orienting response was measured by cardiac deceleration, while effort was measured using the RZ interval (RZI), which is the time interval between the R peak, which reflects ventricular depolarization, and the Z point, which represents the maximum speed of aortic blood flow. Regarding the orienting account of PES, a larger cardiac deceleration in errors was expected compared to correct responses. On the other hand, regarding the effort account of PES, a decrease in RZI after errors was expected, compared to correct responses. This is because RZI is an index of the preejection period (PEP) which reflects the sympathetic effect on the contractility of the heart. Besides, several studies showed that PEP becomes shorter with increased task difficulty, rendering it a reliable index of cognitive effort.

Results did not show a positive correlation between cardiac deceleration and PES, but they did show a decrease in RZI during posterror trials. Therefore, these findings support the idea of an increased effort in post-error trials, promoting the cognitive control account of PES.

Research has studied the influence of positive and negative feedback on heart rate.

Somsen et al. (2000) [62] used the Wisconsin Card Sorting Task and showed that the cardiac slowing following a response depended on the nature of the feedback. Indeed, negative feedback was associated with larger cardiac deceleration than positive feedback. In addition to this response concerning the valence of the feedback, cardiac slowing to negative feedback was larger when the feedback occurred after a rule change, meaning that the information value of the feedback also had an impact on the cardiac deceleration amplitude. From these findings, Somsen et al. (2000) concluded that heart rate deceleration following negative feedback is influenced by both information value, which gives the subject an opportunity to adjust their responses in the subsequent trials, and by a mismatch between the expected and the actual received feedback.

Van der Veen et al. (2004) [72] tested this hypothesis and included a yoked-control condition, in which the received feedback had no relation to the performance nor any information value. As expected, there was a heart rate slowing following negative feedback, however, this deceleration did not show any differences between the experimental and the yoked-control conditions. This challenges the interpretation given by Somsen et al. (2000), because it suggests that neither the information value nor the mismatch between expected and received feedback has an effect in the cardiac deceleration amplitude. Therefore, Van der Veen et al. (2004) suggested that heart rate deceleration following negative feedback simply reflects the valence of the feedback, meaning that this slowing occurs every time negative feedback is presented.

Crone et al. (2003) [60] investigated these two opposing hypotheses using the probabilistic learning task. This task required that subjects pressed the left versus right key in response to six stimuli. Each response was followed by a positive or negative feedback and subjects had to infer the stimulus-response mapping rule by trial-and-error, using information provided by the feedback. There were 3 conditions: on the 100% mapping condition, two stimuli were always mapped onto the left versus right key, meaning that the feedback was 100% useful. On the 50% mapping condition, feedback was unrelated to the chosen key, providing 50% positive and 50% negative feedback. Lastly, on the always condition, the two remaining stimuli provided always-positive or always-negative feedback, independently of the chosen key. Results showed that negative feedback was associated with heart rate deceleration in the 100% condition. Furthermore, heart rate decelerated after positive and negative feedback in the 50% condition, but only when feedback was different from the feedback on the previous stimulus encounter. Lastly, heart rate did not show differences between positive and negative feedback in the always condition. In agreement with Somsen et al. (2000), the authors suggested that heart rate slowing following feedback is caused by a mismatch between the expected and the received feedback. Therefore, they disconfirmed the hypothesis suggested by Van der Veen et al. (2000).

A study by Hajcak et al. (2003) [61] used a Stroop task, in which negative feedback was not provided, and extended the results by Somsen et al. (2000) [62]. They found that heart rate decelerated following errors, even in the absence of feedback, suggesting that the cardiac deceleration reflects also internal processes associated with response monitoring.

2.3 The Importance of Response Certainty

Decision confidence refers to the degree of certainty or confidence that the response made is correct [73, 74, 75], while decision uncertainty is the complementary probability of an unsuccessful outcome. Certainty is very important in daily life as it helps to make informed decisions even in a complicated environment. Besides, it affects how the following actions are conducted and how to learn from past errors, especially when subsequent decisions depend on each other [76]. Unfortunately, the process of extracting decision confidence from behavioural and neurophysiological data is very complicated, as all these concepts are interrelated.

The most common way to assess decision uncertainty when conducting an experiment that involves a decision-making task is to ask the subjects to indicate how certain they feel about the accuracy of that decision. The question that follows up this information is how do the subjects themselves know how to evaluate their degree of certainty in a decision. Several hypotheses have been proposed but there is no unanimous explanation as of yet [77]. A property that has been associated with decision certainty is the quality or strength of the stimulus, which refers to the discriminability of the stimulus. For example, in a dot motion direction-discrimination task, stimulus strength is changed by varying the proportion of dots moving coherently in the same direction: increasing the proportion of dots moving in the same direction, will increase the strength of the stimulus. Another example of stimulus strength could be related to contrast, that is, low contrast stimuli are often weaker than high contrast stimuli. Increasing the strength of a stimulus or the discriminability between stimuli is reported to decrease response time and increase response accuracy [78]. This property can therefore be changed to modulate the difficulty of the task, for example by changing the salience of the stimulus or by changing the stimulus presentation time.

Several models of confidence that are based on signal detection theory (SDT) assume that when a decision is correct, confidence is positively correlated with evidence strength. On the other hand, when the decision is wrong, this correlation is negative [51, 77]. The explanation for this prediction is represented in Figure 2.1.

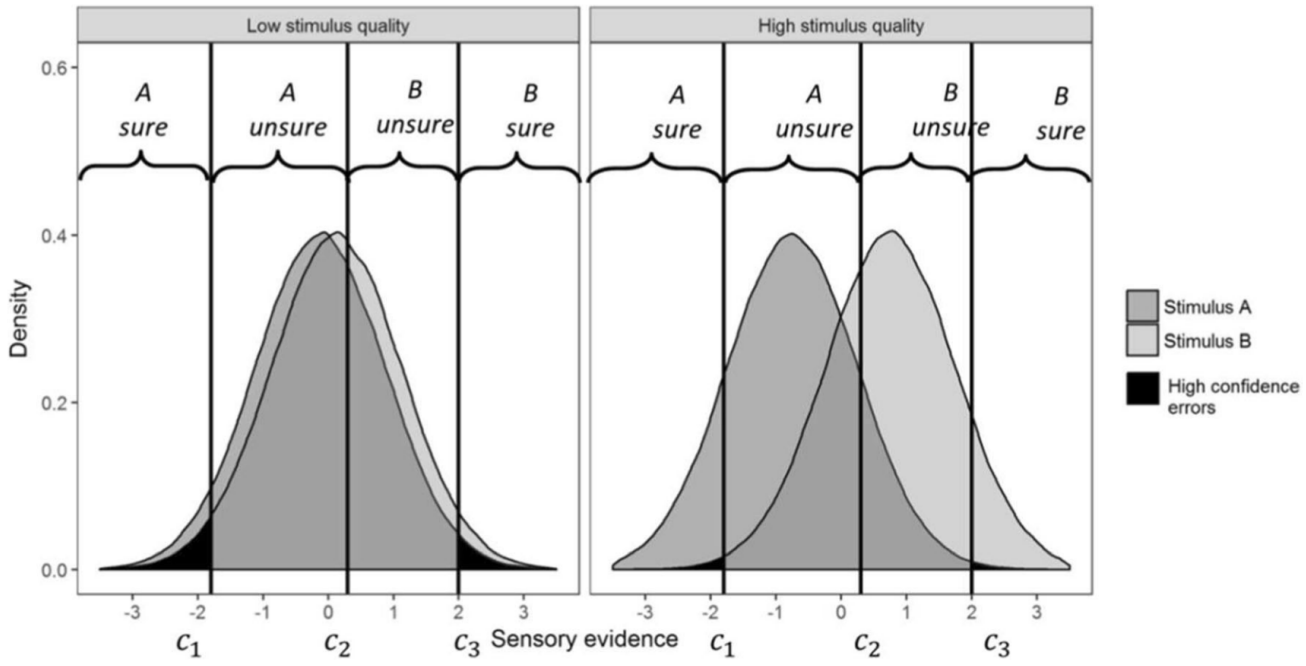


Figure 2.1: Distribution of evidence as a function of how different the stimuli are. Reprinted from [77].

When a subject makes a decision, their confidence on the decision is based on the amount of evidence there is available. In order to be confident on the decision, this evidence needs to surpass a certain criterion that separates decisions without confidence from decisions with confidence.

In tasks which require the subject to distinguish between two stimuli, when the discriminability of the stimuli is low, making them appear very similar and indistinguishable, the distributions of evidence overlap, as can be seen in the left section of Figure 2.1. In contrast, when the discriminability of the stimuli is high, these distributions become more distant from each other, as seen in the right section of Figure 2.1. When this is the case, the distance between portions of evidence distribution that don't overlap becomes larger, resulting in a higher likelihood of the decision being correct. If this distance is too large, the portions of the distributions exceeding the confidence criteria for wrong decisions will become too small (black segments in Figure 2.1), which means that confidence in wrong decisions will be diminished [77].

It is, however, important to understand that this pattern has not been observed in every experiment conducted so far, showing inconsistent results depending on the task [77].

Apart from this evidence, it has been proposed that another source of information that helps to establish a degree of confidence is the decision time [74]. In fact, a long decision time is frequently associated with poorer evidence and increased number of errors. Therefore, the brain may learn to use decision time as an index for quality of stimulus in judging certainty. However, SDT and most models have not been able to involve this variable in the decision-making process. Kiani et al. (2014) [74] showed that certainty not only depends on evidence, but also on decision time. Their findings showed that certainty is inversely correlated with reaction time, and that this correlation was preserved even for error responses, which contradicts existing explanations of certainty based on signal detection theory. These findings suggested that decision time is a factor in certainty judgement because it operates as an index of task difficulty.

Not much is known about the role of the brain in decision uncertainty. The mechanisms that convert decision uncertainty into subsequent adjustments remain unclear. One hypothesis is that the brain signals uncertainty to the neural circuits through the arousal systems, which in turn recruit neurotransmitters and change the global state of the brain [52, 51]. These uncertainty-related changes can then be translated into behavioural adjustments. The neuromodulators that are involved in implementing uncertainty in the brain are acetylcholine and norepinephrine [79, 80]. Acetylcholine is said to be responsible for signaling unexpected uncertainty, while norepinephrine signals expected uncertainty [80].

Apart from properties related directly to the stimulus, there could be subject-related factors that modulate decision confidence in tasks. Distraction and fluctuations in attention, for example caused by self-generated thoughts, could have an effect on decision certainty.

2.3.1 Pupil Dilation as a Marker of Decision Uncertainty

The relationship between uncertainty and pupil diameter, during decision making tasks, is not fully understood nor extensively studied. Pupil diameter has been linked to decision uncertainty, with an increased pupil diameter in response to conditions of uncertainty [54, 55, 81, 82].

Particularly, Brunye et al. (2017) [81] studied pupil diameter over time, under different levels of uncertainty, while participants viewed stimulus images in a decision-making task. The mean changes in pupil diameter, as a function of three levels of certainty, are represented in Figure 2.2.

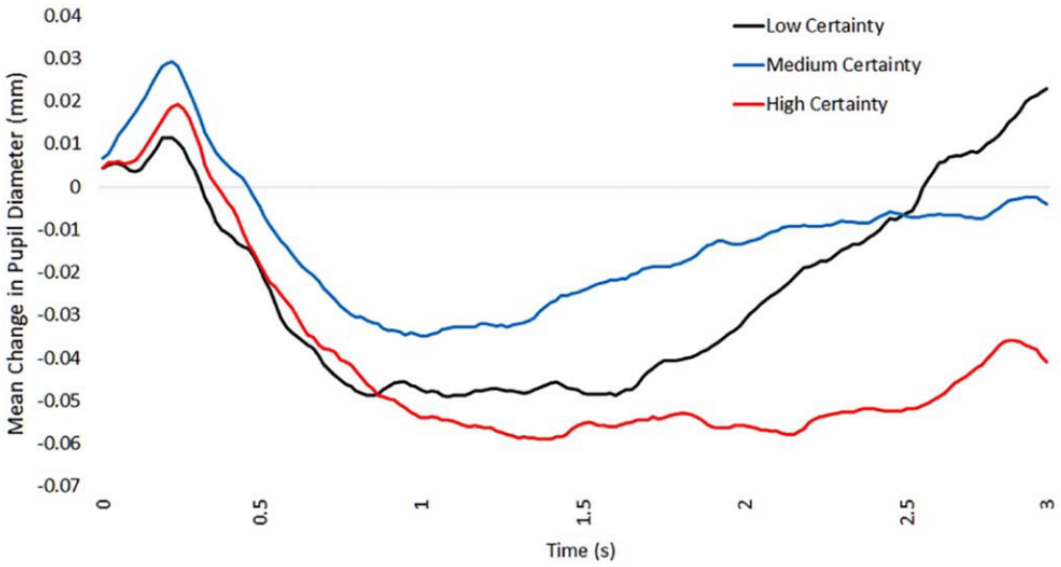


Figure 2.2: Mean change in pupil diameter (in millimeters) over time while viewing stimulus images, as a function of the three certainty levels (low, medium, high). Reprinted from [81].

During stimulus-viewing and in the high certainty condition, no significant increases in pupil diameter were reported. In medium certainty trials, there appears to be an increase in dilation, starting around 1 second after stimulus onset. Lastly, under conditions of low certainty, there was a significant dilation response, however it only started around 2 seconds after stimulus onset. These results are in line with some theories of pupil dilation that propose that the process of changing from an exploration state to an exploitation state is reflected by pupil diameter changes. Indeed, in this study and under conditions of high certainty, it seems that subjects switch from an exploration to exploitation state immediately after stimulus onset. In contrast, when in low certainty conditions, this switch seems to occur just before the response. This temporal difference is unlikely to be related with motor response, as this should be similar in all conditions, but it could be due to cognitive effort. For instance, when under uncertain and difficult conditions, there might be less evidence, and therefore it takes longer to make a decision. However, it is hard to interpret these results because visual stimuli affect the pupil size.

Contrary to the previous study, Urai et al. (2017) [51] studied the uncertainty-related pupil dilation and found a relatively monotonic increasing of pupil dilation. This, however, was examined in different time moments, specifically after the decision and immediately prior to feedback.

In the same study, Urai et al. (2017) [51], used a statistical model which pre-

dicts three signatures of decision uncertainty. One of the signatures was explained in subsection 2.3 and it proposes that decision uncertainty decreases with evidence strength for correct choices but increases with evidence strength for incorrect choices. The other two characteristics predicted by this model are that uncertainty predicts a monotonic decrease in response accuracy from 100 to 50% and that higher uncertainty predicts worse response accuracy, even in conditions of equal evidence strength. All these correlations are represented in Figure 2.3.

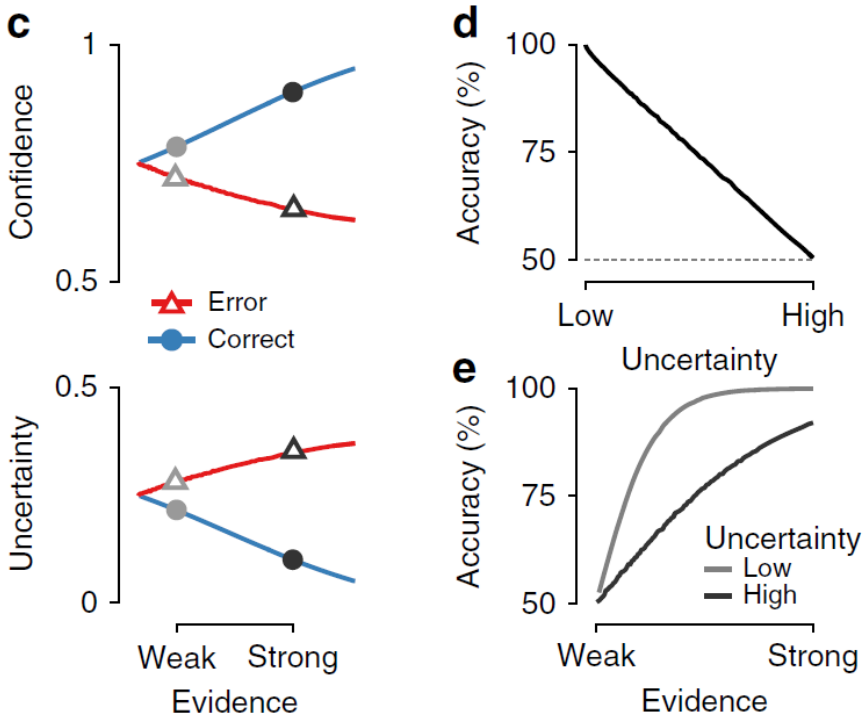


Figure 2.3: Three signatures of decision uncertainty. Reprinted from [51].

Regarding reaction time, it presented all three signatures of decision uncertainty, in agreement with other studies. Regarding pupil diameter, it increased during decision formation, reaching its highest size immediately after the response, which is in line with another study [83]. Furthermore, pupil size increased again after feedback. Between these two moments, i.e. after response but before feedback, pupil dilation presented the three signatures as predicted by the model.

Another goal of this study [51] was to test if uncertainty-related pupil responses predicted behaviour changes in the following choice trials. Indeed, this was confirmed because results showed that when a response was followed by a small pupil response, subjects tended to repeat the same response in the following trial. In contrast, when the previous pupillary response was larger, this bias was not present. A similar effect

was observed with regard to the previous trial reaction time: if the previous response was made quickly, subjects tended to repeat the same choice, but the same did not happen when the previous response was slow.

Colizoli et al. (2018) [52] reproduced this scaling of pupil responses with decision uncertainty before feedback and assessed if the same scaling of pupil responses occurred after feedback. For this post-feedback interval, predictions were generated for the complement of prediction error, as represented in Figure 2.4, with the prediction error being the difference between expected and actually received reward after receiving feedback. In line with this prediction, pupil response during post-feedback scaled with uncertainty-dependent prediction errors.

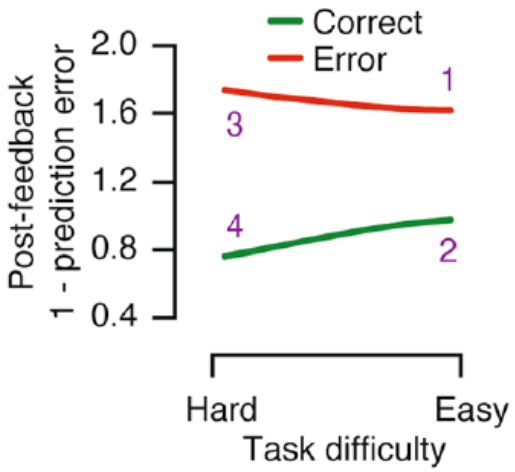


Figure 2.4: Prediction error as a function of task difficulty during the post-feedback interval. Reprinted from [52].

Besides, in the same study [52], the data of the post-feedback responses from Urai et al. (2017) [51] were analysed, for comparison. Similarly, post-feedback pupillary responses were larger after negative than positive feedback. However, the scaling of the responses was different. Indeed, instead of the negative interaction effect between accuracy and difficulty, the interaction in Urai et al. (2017) after feedback was positive. The authors suggested that this could be due to the fact that participants in Colizoli et al. (2018) received a monetary compensation, which was dependent on their performance. In contrast, subjects in the study conducted by Urai et al. (2017) did not receive any monetary reward. Therefore, it could be possible that monetary compensation is needed for the recruitment of pupil-linked arousal systems by uncertainty-dependent prediction errors. In addition to this, other differences may have contributed for the distinct results observed between the studies, such as the task itself, the delay periods and the groups of participants.

Similarly to Urai et al. (2017), Gee et al. (2017) [84] showed that in decision-making tasks, when pupil responses are larger, the decision bias is reduced. This bias refers to the tendency that a subject has to make a decision without paying significant attention to the available evidence. Therefore, this bias reduction predicted by large pupil dilation supports the idea that phasic activity during decision-making optimizes behaviour. The authors concluded that when there is uncertainty regarding a decision, not only it is important to track the evidence used to make the decision, but it is also important to track phasic arousal signals, such as pupil dilation, because these findings demonstrated that phasic arousal plays a significant role in the variability of choice behaviour.

Not much is known about the effect of uncertainty in heart responses. However, given the relationship between heart rate and error awareness and given that error awareness and uncertainty arise from the same cognitive process, it is expected that there is also a relation between heart rate and uncertainty, which will be one of the targets of this study.

2.4 Materials and Methods

As explained in the Introduction (see Section **1**), I did not have the opportunity to take on this project until its completion. However, we were able to develop the experimental paradigm, to test the overall methodology of acquisition using the available equipment in the laboratory, and to acquire some preliminary data which made me familiarized with the preprocessing steps.

2.4.1 EyeLink 1000 Eye Tracker

EyeLink 1000 Plus is the stationary eye-tracking system that is used in the current work to record eye movement data.

This eye tracking system can be mounted in several configurations. The one used here is the Desktop Mount configuration, in which the eye tracker sits below the Display PC in which the participant sees the stimulus during the experiment. This configuration supports monocular, binocular and remote (monocular) eye tracking at several different sampling rates, but here we will be using monocular eye tracking at 1000 Hz sampling rate. This allows highly accurate monocular data to be acquired, of the left or right pupil, using a chinrest. Eye position is calibrated and validated once, at the start of each scanning session.

The EyeLink setup consists of two computers: the Host PC, which is allocated to data collection, and the Display PC, which is used for stimulus presentation. These computers are connected via Ethernet which allows communication of information, such as sharing images from the camera or the occurrence of eye events. These events can be saved in a data file on the Host PC and sent through the Ethernet link to the Display PC.

2.4.2 SynAmps RT 64-channel Amplifier and CURRY 7 Neuroimaging Suite Software

The CURRY Neuroimaging Suite was used to acquire the ECG and it can be seen as a toolbox for data acquisition, analysis, and multi-modal neuroimaging.

This program has several options of license available:

X – Scan-ESI Acquisition

S – Signal Processing

B – Basic Source Analysis

V – Video Recording

For example, an "SBA" license means that there is access to Signal Processing and Basic and Advanced Source Analysis. The software that is owned by our laboratory only has the Acquisition functionality, as marked by "X".

The Acquisition module of CURRY is used to acquire data from many of the amplifier systems produced by Compumedics/Neuroscan, including SynAmps RT.

The amplifier we have available is the SynAmps RT 64-channel Amplifier. This amplifier allows for discrete monopolar and bipolar channels. It has one headbox, comprising of 64 monopolar channels, 4 bipolar channels and 2 High Level Input (HLI) channels. It has a maximum sampling rate of 20000 Hz and a 24-bit resolution.

For this work, the third bipolar channel was used to record the electrocardiogram (EKG), with a sampling frequency of 1000 Hz.

For ease of placement, the 2 electrodes used may be placed along the midline of the chest [85]. The electrode connected to EKG+ was placed above the plane of the heart and the electrode connected to EKG- was placed below the plane of the heart.

After placing the electrodes, connecting them to the amplifier and choosing the

preferable configuration, it is possible to choose the path/file name and start recording the electrocardiogram.

2.4.3 Tasks and Procedure

We developed 2 random dot motion tasks in Matlab, using Psychtoolbox-3, in order to study the modulation of arousal (assessed through pupillography) during decision-making under different levels of uncertainty. These tasks were adapted from the tasks develped by Colizoli et al. (2018) [52], who made their code available here: `https://github.com/colizoli/pupil_belief_states`.

These tasks are presented in a monitor, which has a width of 52.5 cm and a height of 39.5 cm, and is at a 90 cm distance from the participant's eyes. In addition, the monitor has a spatial resolution of 1440 x 1080 pixels and a refresh rate of 100 Hz. Dot motion stimuli were presented within a central annulus that was not visible to the subjects (grey background, outer diameter 16.8°, inner diameter of 2.4°). The fixation region was in the center of the annulus and consisted of a grey cross with a white dot at the center, surrounded by a white circle, so that the color of the cross matched the cross of the background of the task. Signal dots moved at 7.5°/s in one of two directions (90° or 270°). Noise dots were randomly assigned to locations within the annulus on each frame, preventing them from being trackable. Each frame consisted of 524 white dots (0.15° in diameter).

First of all, a random dot motion task is a task in which participants monitor a patch of incoherently moving dots in the leftward or rightward direction. The movement of these dots can take different coherence levels; for example, a coherence of 25% indicates that 25% of the dots are moving together in a given direction.

In our study, the experiment starts with a threshold session, which has 5 coherence levels, and is followed by a main experimental session, which has 3 coherence levels. The importance of having different difficulty levels is that it allows us to assess whether the older group is able to increase their arousal to fully meet the demands of the the most difficult levels. If they fail to do this, it means that these differences in arousal modulation between groups may underlie the age-related deficits commonly found in decision-making tasks.

During both tasks, subjects are instructed to press the key that corresponds to the direction of the coherent dot motion (key z for left motion and key m for right motion), using the index fingers of both hands. This response is followed by auditory feedback. Subjects must keep fixation in a central target during the entire task, as

seen in Figure 2.5.

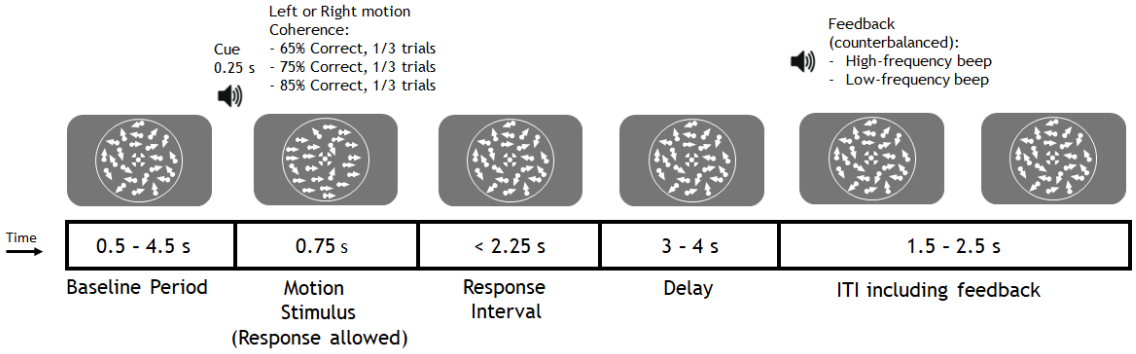


Figure 2.5: Schematic of the dot motion task (adapted from [52]).

Each trial is composed by 5 stages during which random motion (0% coherence) is presented, except during the stimulus interval: 1) pupil baseline period (0.5-4.5 s), 2) stimulus interval which consists of coherent motion, during which response is allowed (0.75 s), 3) response window, which is the second period during which participants are allowed to respond (maximum duration is 2.25 s), 4) delay period before feedback (3-4 s), 5) feedback and the inter-trial interval (1.5-2.5 s). The onset of the stimulus coincides with an auditory cue, which is presented for 0.25 s (pure tone at 880 Hz). Auditory feedback is counterbalanced across participants: for even-numbered participants, a high-frequency tone (1080 Hz) means a correct answer, while a low-frequency tone (680 Hz) means a wrong answer; for odd-numbered participants, this is switched. In the threshold session, the task itself forces participants to respond in every single trial, even if this implies a slower answer, while in the main experiment, a response is not mandatory. In situations in which the subject does not respond within the imposed time interval, a "no answer" auditory file is played and the task moves on to the next trial.

The threshold session consists of 2 blocks of 50 trials per coherence level (0%, 2.5%, 5%, 10%, 20%), yielding a total of 250 trials per block, 500 trials total. The data acquired in this session was fit with a psychometric function with 5 levels in order to determine 3 coherence levels that yield accuracy levels of 65% (Hard), 75% (Medium) and 85% (Easy), respectively. These final coherence levels, which are individually titrated, are used and kept constant during the main experiment. During this session, immediately after each response, an auditory feedback is played, which is counterbalanced across participants.

The main experiment consists of blocks of 90 trials, with 30 trials per coherence level. Here, 3-6 blocks would be acquired to yield a sufficient number of trials for

analysis. During this session, an auditory feedback is played after a variable delay of 3-4 seconds, which is counterbalanced across participants.

2.4.3.1 Methodology

The overall procedure for the designed experiment consists of the following steps:

- Clean the area of the chest of the subject where the electrodes are going to be placed, for the recording of the ECG, using alcohol soaked cotton balls.
- Use a needle to insert gel in the 2 electrodes.
- Placing of the 2 electrodes along the midline of the subject's chest, using adhesive tape.
- The subject sits on a chair in such a way that his or her face is around 90 cm from the screen, placed on a head-stabiliser and in such a way that the electrodes connect to the SynAmps RT 64-Channel amplifier.
- Explanation of the test session and statement of instructions by the experimenter. The instructions have to be identical for all subjects, and they are presented both orally and written on the screen.
- Make sure that the eye is on focus on the screen.
- Calibration of the eye tracker (between 3 and 25 points across the screen). The calibration has to be carried out at the beginning of each block. If it does not work, the data cannot be recorded and the participant has to be excluded.
- Validation of the information acquired during calibration.
- Start recording the ECG in the Neuroscan Curry 7 software.
- Measurement(s), while the subject performs the two-alternative forced choice tasks.
- Stop recording the ECG in the Neuroscan Curry 7 software.

Throughout this whole process, it is important to allow the participant to rest and take breaks since pupil size is sensitive to fatigue, as explained in subsection 1.3.1. Before this process, it is also advisable to run several training trials to ensure that the subject understands the instructions.

2.4.3.2 Data Pre-processing

As mentioned, some data was acquired in order to familiarise with the pre-processing of heart rate and pupil data.

At the end of the ECG recording, 4 files are generated in the following formats: .ceo, .dap, .dat and .rs3. Using Matlab, we called the *loadcurry()* function, which takes the .dap or the .rs3 file as an input, and exports data in the .txt format. Then, we used the QRSTool [86], which is a software that calculates several metrics of cardiac variability. It imports the ECG signal text file, finds the R-waves, and then exports a .qrs file. Afterwards, we use a Matlab custom script that imports this file and outputs 3 variables: *qrs_beat_data*, *qrs_ecg_data* and *qrs_event_data*, which are data scrutures with information regarding the beat data, the ECG data and the task events. We also use a script that creates and outputs the IBI (interbeat interval) timeseries and the HR (heart rate) timeseries. Lastly, we have a script that imports the ECG triggers, its timestamps and the HR timeseries, removes all data before the trigger correspondent to the start of acquisition, and creates a matrix with the triggers and the HR data, which can then be loaded to EEGLAB [87]. EEGLAB returns a dataset (.set), which can then be target of further analysis.

At the end of acquisition, the EyeLink 1000 API returns an .edf file. This file contains many types of data, such as eye movement events and messages that were inserted in the Matlab task script. We then used an EDF Converter (SR Research), which is a program that creates .asc files from .edf files. Finally, we go back to Matlab, where we use a script file adapted from Urai et al. (2017) [51], that reads in the .asc EyeLink file, extracts triggers from messages, linear interpolates the blink artifacts, regresses out pupil responses to blinks and saccades, and creates data that can be used in EEGLAB [87]. Once again, by importing this data to EEGLAB, it returns a dataset (.set) that can then be target of further analysis.

An overview of these steps is visually presented in Figures 2.6 and 2.7.

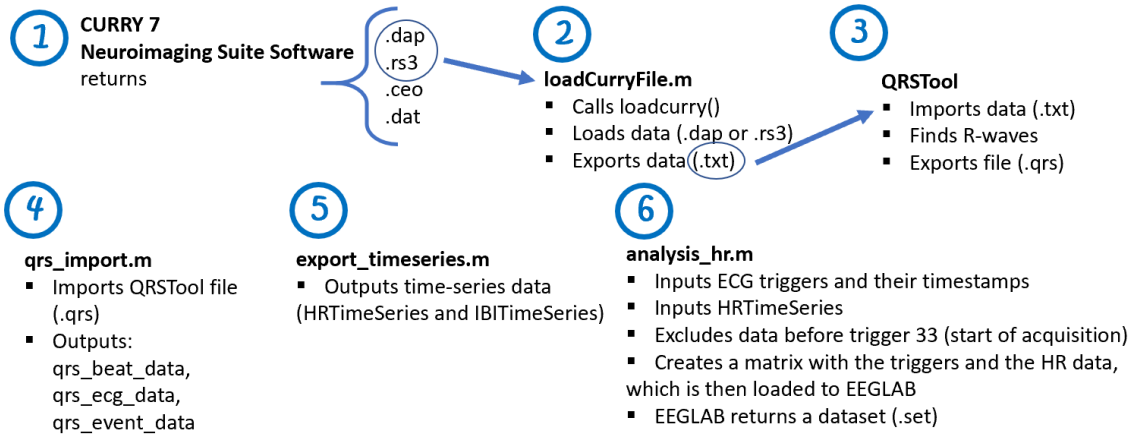


Figure 2.6: Schematic of the steps required to pre-process ECG data.

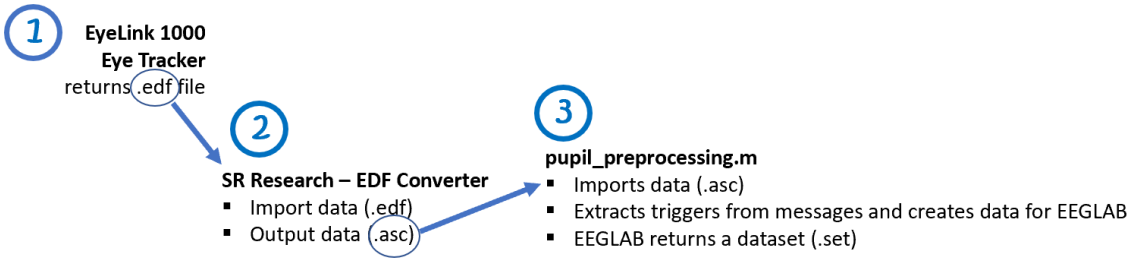


Figure 2.7: Schematic of the steps required to pre-process pupil data.

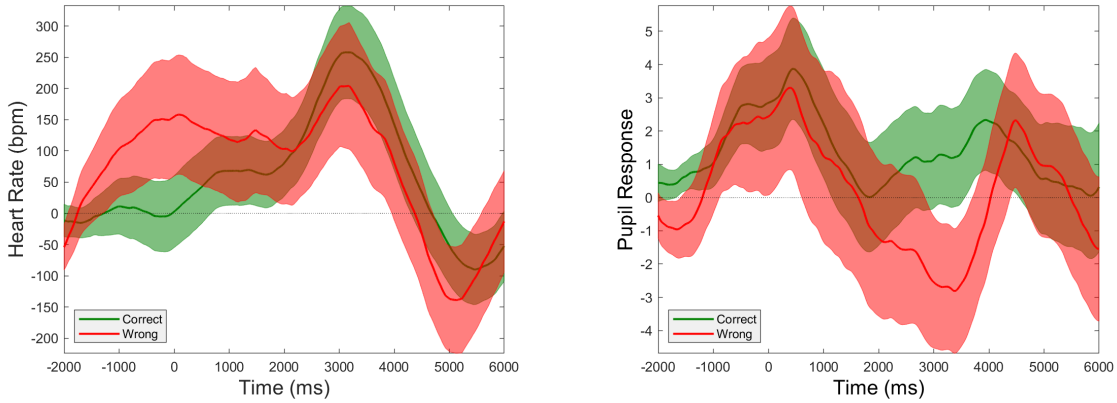
2.5 Preliminary Results

In this section, we will go over the results obtained for the single subject (age 22y) that performed this task while their pupillogram and ECG were being recorded.

In the threshold section, the subject performed 490 trials, separated in 7 blocks. Therefore, there were 98 trials correspondent to each coherence level (0%, 2.5%, 5%, 10%, 20%). The three coherence levels that yielded accuracy levels of 65%, 75% and 85% were 3%, 5% and 8%, respectively. Then, we used these three coherence levels to perform the main task. The main task was composed of 120 trials, separated in 2 blocks. The subject missed 2 trials, therefore there were a total of 118 trials. Regarding their behaviour, the subject responded correctly on 68.64% of the trials, and got 31.36% of the trials wrong. As expected, their accuracy improved with coherence level: they got 56.41% of the trials correct for a coherence of 3%, 72.50% of the trials correct for a coherence of 5%, and 76.92% of the trials correct for a coherence of 8%.

In the following figures, we represent the HR as a function of time, in a response-

locked waveform. The HR was analysed by merging the datasets of both blocks, cutting the resultant signal into epochs locked to response onset from -2000 ms until 6000 ms, and removing average baseline activity from each trial (set from -1000 ms to cue onset). We also represent the pupil response, in a response-locked waveform. Similarly, pupil response was analysed by merging the datasets of both blocks, cutting the resultant signal into epochs locked to response onset from -2000 ms until 6000 ms, and removing average baseline activity from each trial (set from -500 ms to cue onset).

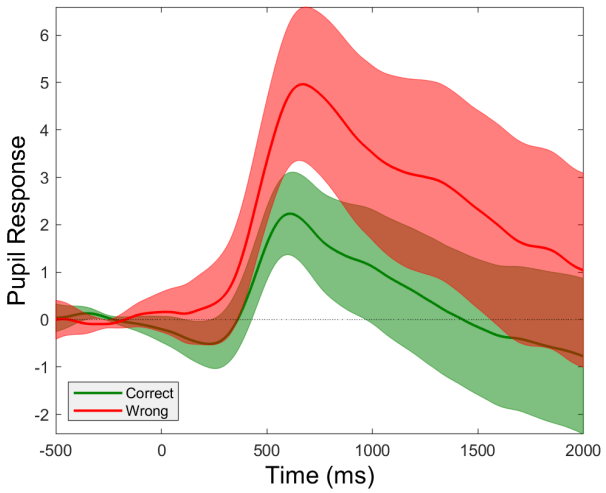


(a) **(b)**

Figure 2.8: a) Response-locked HR time course, separated by correct and wrong responses. b) Response-locked pupil dilation time course, separated by correct and wrong responses.

These figures do not show clear differences in the signals between correct and wrong trials, at the moment of response. However, we can confidently say that there is an increase in both signals after motor response, which is in agreement with previous studies. Specifically, they increase after response onset and decrease following feedback.

We also represent the pupil response in the feedback-locked waveform, being that in these epochs, the baseline removed was set from -500 ms to feedback onset. After feedback, we can see that the pupil increases more after wrong responses than correct responses. This is in agreement with the literature, which has shown that errors during a decision-making task elicit an increase in pupil diameter.



(a)

Figure 2.9: Pupil dilation time course, using the feedback-locked waveform, separated by correct and wrong trials.

Future work, with a larger amount of subjects, is needed to present more reliable results. For instance, with more data it could be possible to fully assess how HR and pupil response change with task difficulty, that is, with the coherence levels of the dots, since it is known that these physiological signals tend to change according to the task demands. Furthermore, with data from older subjects, we could investigate if this modulation with task demands is preserved with ageing.

By adding the response certainty scale feature to the task, it would be interesting to see how responses change based on whether errors are perceived or not, and based on how certain or uncertain the subject is on their response.

Overall, a larger amount of data belonging to both younger and older adults would allow us to assess the mechanisms of error monitoring, response certainty, task performance, and to investigate how all of these change with arousal and ageing.

3

ERP Markers of Evidence Accumulation during Perceptual Decision-making, their Modulation by Arousal, and Age-related Changes

3.1 Project Aims

The evidence accumulation process of decision-making refers to the process by which noisy sensory information is accumulated until sufficient evidence has accrued to favor one decision over another. The event-related potential (ERP) centro-parietal positivity (CPP) is a neural correlate of this sensory evidence accumulation that can be studied in the electroencephalogram (EEG). It has been shown to present several features of an accumulator, such as having a slope that increases with response time, differentiating between easy and difficult trials, differentiating between correct and wrong trials, and predicting the upcoming choice. This potential is also known to increase until response latency, and its amplitude has been shown to reach a threshold level which is irrespective of reaction time.

Since our main goal is to study the effect of ageing on the arousal system and its consequences on the cognitive level, we decided to investigate the effect of ageing on evidence accumulation, and to assess if modulation by arousal levels during this process differs between younger and older adults.

Previous studies on evidence accumulation models have mostly focused on exploring the arousal system and the CPP in visual decision-making tasks and on younger

subjects. Here, we intend to study these mechanisms using data acquired during a decision-making auditory task, and to investigate whether there is also a relationship between arousal and evidence accumulation in older adults. In order to do this, we will investigate whether pupil-linked arousal and task performance have an effect on the CPP build-up rate. In addition, we intend to investigate the relationship between task performance and pupil dynamics.

To achieve these goals, we first investigated the relationship between pupil-linked arousal and behavioural performance, particularly the reaction time (RT), and whether this relationship was affected by ageing. Then, we performed analyses to find out how the slope of the CPP, which represents the rate of evidence accumulation, changes with three variables: the RT, the preparatory pupil response and the baseline pupil diameter, and once again whether these relationships change with ageing. We also did time point-by-time point correlation analyses between the CPP and these three variables to find out in which time windows of our data there is a significant correlation between the CPP and the three variables being analysed. In addition, we assessed if the CNV, a frontocentral potential that occurs in the interval between the presentation of a cue and a target, has an effect on the build-up rate of the CPP and on the RT. In all of the mentioned analyses, we performed statistical tests to investigate if there was an effect of group, task and/or an interaction group $\times$ task.

3.2 Evidence Accumulation Models

The accumulation of evidence over time is a major component of both cognitive function and mathematical models for decision making. This concept originated from a neurophysiological study in monkeys, in which they were trained to discriminate the direction of motion in a random-dot visual display. The results showed that parietal areas accumulate evidence during perceptual decisions [88]. Since then, there has been tremendous progress in characterizing the accumulation of neural information in perceptual decision-making, and mathematical models of evidence accumulation have proven to be very successful in doing so.

According to all accumulator models of decision making, the brain makes decisions by accumulating noisy sensory evidence over time until this evidence reaches a threshold corresponding to one of the different decision alternatives [89, 90, 91].

Almost all of these models employ common latent variables, such as the quantity of evidence needed to trigger commitment (the decision boundary), the rate of evidence

accumulation (the drift rate) and mechanisms not directly associated with evidence accumulation, such as sensory encoding and motor execution (the non-decision time) [89].

Two commonly used models that attribute decisions to an evidence accumulation process are the Drift Diffusion Model (DDM) and the Linear Ballistic Accumulator (LBA) model. The DDM and the LBA models are schematized in Figure 3.1 and 3.2 respectively. According to the DDM, for a two-alternative forced choice decision, the accumulation of noisy sensory evidence starts at z, with a drift rate ν, until one of the decision boundaries (thresholds) is surpassed, resulting in a decision. The response time corresponds to the sum of the diffusion process and the non-decision time (Ter). On the other hand, the LBA assumes that evidence accumulation for different response alternatives occurs independently. The evidence for each alternative is integrated as a separate total, and the various totals (two in the situation represented in 3.2) race against each other. As a result, the ultimate choice depends on which of the integrators reaches its threshold first.

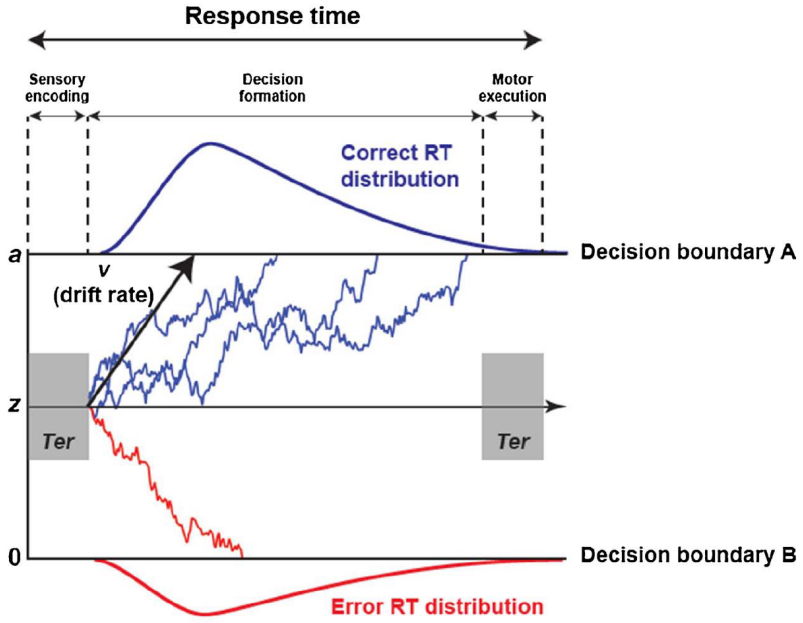


Figure 3.1: Drift Diffusion Model. Reprinted from [89].

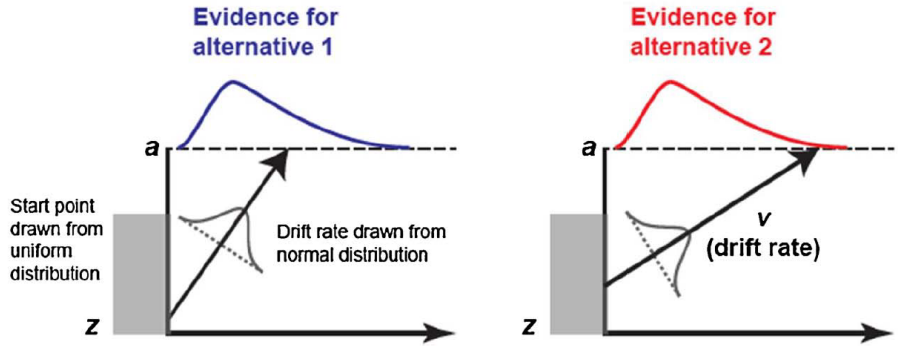


Figure 3.2: Linear Ballistic Accumulator. Reprinted from [89].

3.3 Central-Parietal Positivity

Even though it is difficult to study evidence accumulation using non-invasive functional neuroimaging methods, electroencephalography (EEG) has been shown to be the preferred method. Scalp EEG is a noninvasive and low-cost technique that directly quantifies the electrical activity of the brain at scalp sites with sub-millisecond temporal resolution. Given this resolution, and knowing that several aspects of attention and perception operate on a scale of tens of millisecond, EEG is the most commonly chosen method to examine the neural correlates of evidence accumulation.

A few ways to assess evidence accumulation using EEG are to study event-related potentials (ERP) at specific moments in time, to study ERPs over time or to study the dynamics of brain oscillations.

ERPs are voltages generated in the brain in response to events or stimuli, and they can be recorded while the subject is performing a sensory or cognitive task [92]. These changes in voltage are time locked to sensory, motor or cognitive events and they reflect the neural activity generated in a range of cortical sources which are active during the task. Following signal averaging, ERP waveforms are formed, which are composed of negative and positive deflections. These waveforms are characterized according to latency and amplitude. For instance, the P300 or P3 wave is elicited by a stimulus and shows up approximately 300 ms after a target stimulus. There are other frequently identified ERP components, such as the N1 and the P1, as can be seen in Figure 3.3.

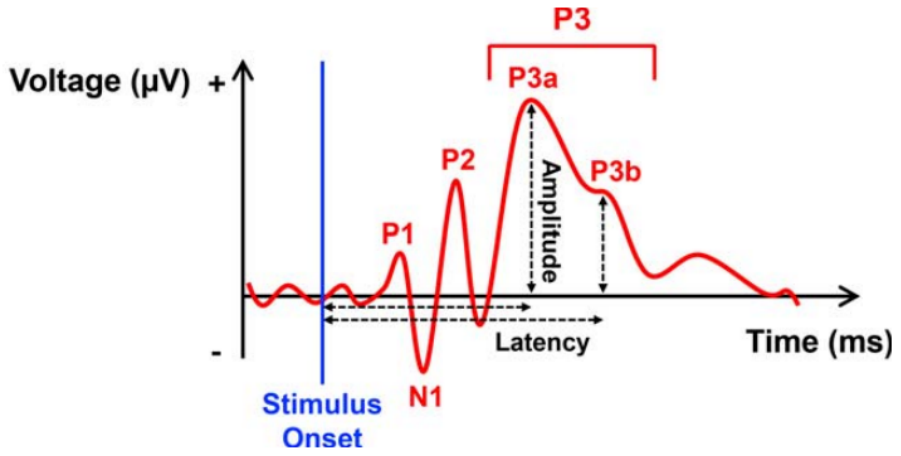


Figure 3.3: A waveform showing several ERP components, including the N100 (labeled N1) and P300 (labeled P3). Adapted from [93].

Another approach to analyse EEG data is to look at brain periodic activity or oscillations, which consist of rhythmic patterns of neural activity generated by a large group of neurons in the central nervous system, in response to stimuli [94]. These oscillations can be characterized by the frequency range in which they occur, e.g., delta, theta, alpha, beta or gamma waves.

In the present study, we will be studying ERPs to assess the neural correlates of the evidence accumulation process. For this reason, in the following paragraphs, we present a brief description of previous studies that have assessed this same process using EEG and, specifically, ERP analyses.

According to accumulator models, a decision variable is characterized by a time course that builds as a cumulative function of sensory evidence and it determines a behaviour via a boundary-crossing criterion (see Figure 3.1 and 3.2). O'Connell et al. (2012) [95] were the first ones to propose a conclusive evidence of a signal that encodes a decision variable. They used a gradual target detection task and conducted ERP analysis, by which they found a signal that exhibited these exact characteristics. They found a centro-parietal positive ERP component (the CPP), which increased with incoming evidence strength and peaked at the response latency. In addition to this, the CPP covaried with reaction time; its build-up increased over time, which suggests that the CPP was specifically indexing the temporal integration of the evidence As mentioned, another property of a decision variable is its boundary-crossing criterion, meaning that the time of decision and response execution is determined by its amplitude reaching a threshold level. Consistent with this, the response-aligned CPP waveform reached a fixed amplitude irrespective of

reaction time. Another feature of this signal is that it seems to behave this way even when a decision is reached but no response is required, meaning that it is independent of motor requirements. Lastly, they pointed out that the CPP shares a lot of common characteristics with the classic P300 ERP component, which was also assessable in their task design. Particularly, they have the same topography (centro-parietal), polarity and dynamics (both of them increase until they peak at response execution).

In their next paper [96], they used a two-alternative dot-motion discrimination task, meaning that participants monitored a patch of incoherently moving dots in the leftward or rightward direction. The coherence level of these dots could take one of four values: 25%, 35%, 50%, or 70%, being that these values represent the percentage of dots moving together in a given direction. The subjects were asked to indicate leftward motion with a left-hand button press and rightward motion with a right-hand button press, as soon as they were sure of the motion direction. Then, the authors measured the build-up rate of the CPP by fitting a straight line to the unfiltered ERP waveform of each subject, using the interval of -250 to -100 ms for the response-aligned CPP, and measuring its slope. They showed that the CPP build-up rate strongly predicted reaction time within coherence levels. In other words, a steeper build-up rate of CPP was associated with a faster RT, within a given coherence level, as can be seen in Figure 3.4.

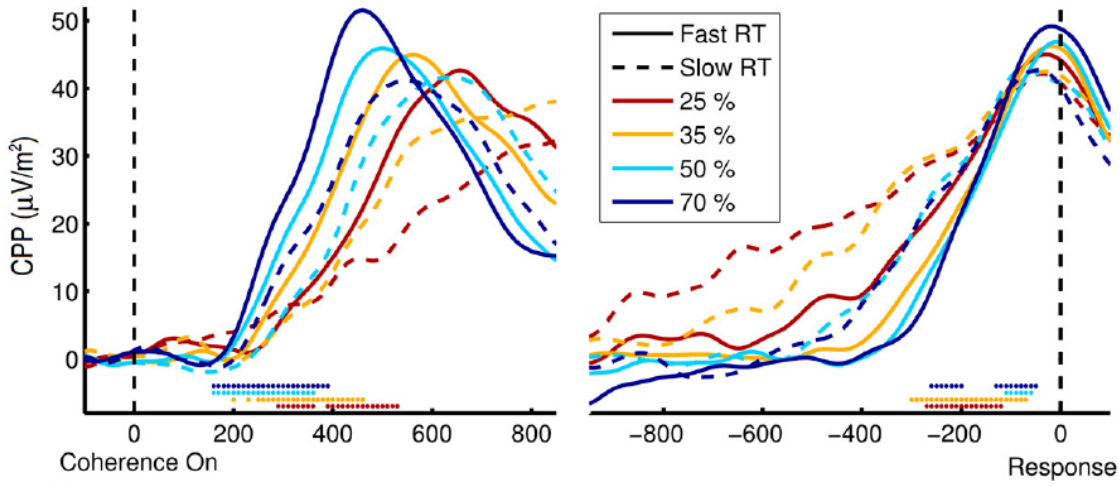


Figure 3.4: CPP waveforms aligned to stimulus onset (left) and response (right) show that faster buildup rates led to faster RTs. Reprinted from [96].

Later, Murphy et al. (2015) [97] used a Go/No-go response inhibition task and observed that this same CPP exhibited a gradual build-up before Go and No-go choices. Consistent with the previous literature, the CPP build-up rate was inversely

proportional to reaction time and it reached a peak amplitude at the time of choice commitment.

Similarly, Pisauro et al. (2017) [91] explored the CPP signal in a value-based decision task, using simultaneous EEG-fMRI. They found similar evidence accumulation dynamics in the same centroparietal electrodes as O'Connell et al. (2012). By using fMRI, they associated this EEG signature with BOLD activity in the posterior medial frontal cortex. These results, which were obtained from value-based decisions, indicate that the CPP is a relatively task-independent signature of evidence accumulation. This is also supported by the several studies that have demonstrated a similarity between the P300 signal and the CPP, since the P300 shows up in both perceptual and memory tasks. Therefore, it is expected that the P300/CPP is observed in memory-based, value-based and perceptual decision tasks.

Another feature of the CPP that has been demonstrated is that its waveform is the same for both visual and auditory decision-making [98, 95]. Twomey et al. (2015) [98] investigated the potential role of the P300 component as a decision variable signal that accumulates evidence to a decision bound. To do this, they used two auditory tasks and one visual task. Consistent with previous literature, they found that the build-up rate of the CPP increased in proportion to the strength of sensory evidence. In other words, a stronger evidence was associated with a steeper build-up rate. Besides, the P300 reached a stereotyped amplitude at the time of response execution and its slope differentiated RT bins such that faster build-up was associated with faster RTs. In addition, the dynamics of the P300 found in the visual task were consistent with those observed in both auditory tasks. Therefore, the P300 component exhibited equivalent accumulation-to-bound properties in both sensory modalities, which establishes the equivalence of the P300 and the CPP.

Overall, across these studies, it is clear that the CPP closely tracks evidence accumulation and that it presents the characteristics associated with a decision variable.

3.4 The CPP in relation to Phasic and Tonic Arousal

Modulations in arousal are regulated by the neuromodulatory systems of the brain. The relationships between arousal, neuromodulation and task behaviour have led researchers to conject that arousal might influence several areas of decision making, such as the accumulation of evidence over time. Particularly, it could affect stimulus encoding, the accumulation of evidence, the decision boundary and the decision reaction time.

Another reason why researchers suggested that the phasic activity of the LC-NE system plays a role in the CPP build-up rate is because this phasic activity underlies the P3 component [99] and, as mentioned before, the P3 and the CPP are very similar components.

Murphy et al. (2014) [20] decided to examine how these parameters of decision making are linked to pupil dynamics. In order to do this, they measured pupil size while subjects performed the random dot motion task, which required two-alternative forced choice decisions.

They found that periods of increased pupil diameter, that is, increased tonic arousal, were characterized by greater variability in the rate of evidence accumulation. In addition, pupil diameter correlated with certain behavioural trends that are diagnostic of change in drift rate variability. Overall, these results suggest that tonic arousal is a plausible underlying factor of changes in drift rate variability, during decision-making tasks.

Another study that investigated the link between evidence accumulation and arousal was conducted by van Kempen et al. (2019) [100], who explored how arousal influences the neural processes that play a role in decision formation. In order to do this, they used a random dot motion task and tested how pupil-linked arousal impacted evidence accumulation signatures, such as the CPP.

In this study, the authors first examined the relationship between pupil dynamics and task performance and found that the baseline pupil diameter showed a relationship with reaction time (RT), a measure of task performance. Indeed, RT was slower on trials with higher baseline arousal levels. The pupil diameter response also presented a relationship with the RT. Best performance, that is, faster RT, was found on trials with the largest pupil responses. Overall, this indicates that both tonic and phasic arousal are predictive of task performance.

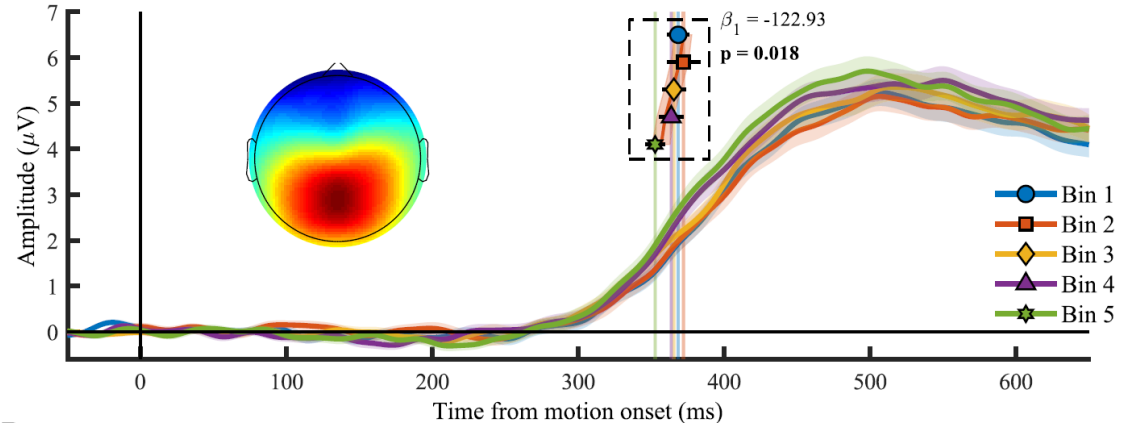
Then, they tested the relationship between the pupil diameter response and the onset, build-up rate, amplitude and inter-trial phase coherence (ITCP) of the CPP. First, it is important to describe the acquisition method of these measures. Onset latency of the CPP was defined as the first time point at which the amplitude was significantly different from zero, using the stimulus-locked CPP waveform. Both CPP build-up rate and amplitude were computed using the response-locked waveform of the CPP. The build-up rate was measured by measuring the slope of a straight line fitted to the CPP in the window from -250 ms to -50 ms before response. The amplitude was defined as the mean amplitude within the 100 ms around the response.

Finally, the ITCP is a measure of across trial consistency in the EEG signal.

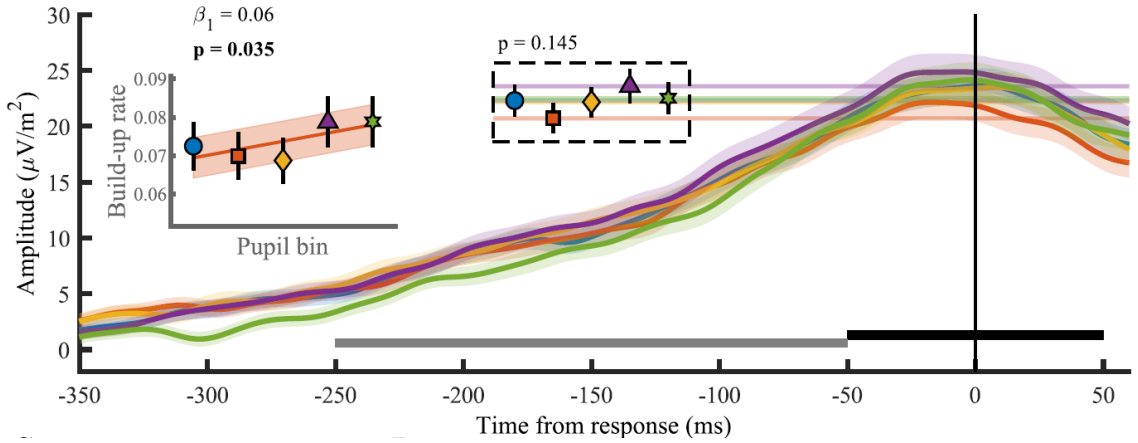
Regarding the results, the CPP showed faster onset latencies for larger pupil response bins, meaning that there was an inverse monotonic relationship between the onset latency of CPP and the pupil diameter response. Similarly, the CPP build-up rate correlated with pupil response, presenting steeper slopes in trials with largest pupil dilations. However, a similar observation was not found for CPP amplitude. Lastly, when examining the ITPC of the CPP, a measure of consistency, they found that the CPP potential is less variable for larger pupil responses. Overall, they reported that the size of the pupil response is predictive of the onset latency, build-up rate and ITPC of the CPP. In other words, larger pupil dilations are associated with faster responses, earlier CPP onset latencies, steeper build-up rates and more consistent CPP. All of these results are graphically represented in Figure 3.4.

On the other hand, the baseline pupil diameter was not predictive of the CPP onset or build-up rate. Instead, it presented an inverse relationship with the amplitude, as well as with the consistency of the CPP. Specifically, they found that higher baseline pupil diameter exhibited lower EEG consistency, which is in agreement with the previously mentioned study by Murphy et al. (2014) [20], which concluded that increased variability in drift rate occurs in periods of increased baseline pupil diameter. Once again, these results can be visually seen in Figure 3.5.

Overall, their results indicate that high arousal is associated with less consistency, i.e. more variability, in the mechanisms underlying decision formation. Interestingly, higher tonic arousal levels are associated with worse performance, which suggests that higher variability in decision processing can negatively impact behavioural performance.



(a)



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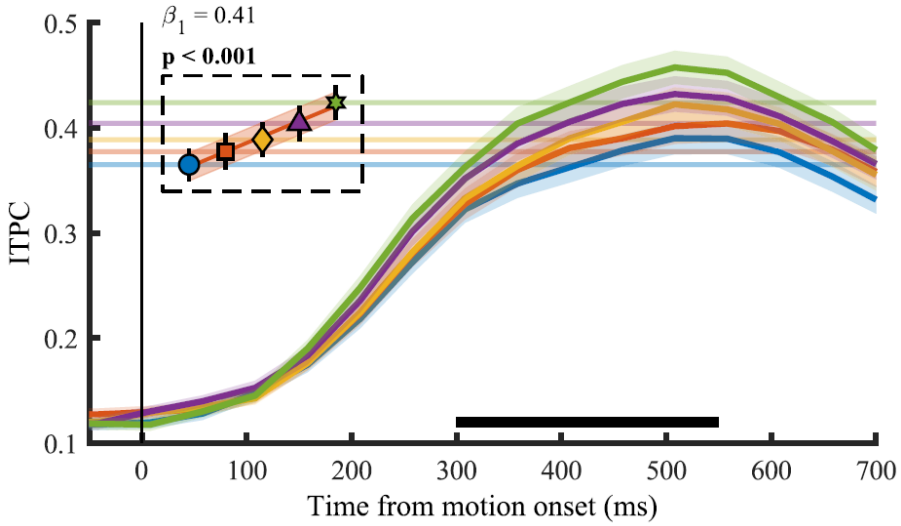


(c)

Figure 3.4: Relationship between pupil diameter, that is, phasic arousal, and the CPP. a) Stimulus-locked CPP, which shows faster onset times for larger pupil response bins; b) Response-locked CSD-transformed CPP time-course, in which the horizontal lines and markers indicate the CPP amplitude, and the inset displays the build-up rate of the CPP across pupil response bins; c) ITPC per pupil bin time. Reprinted from [100].

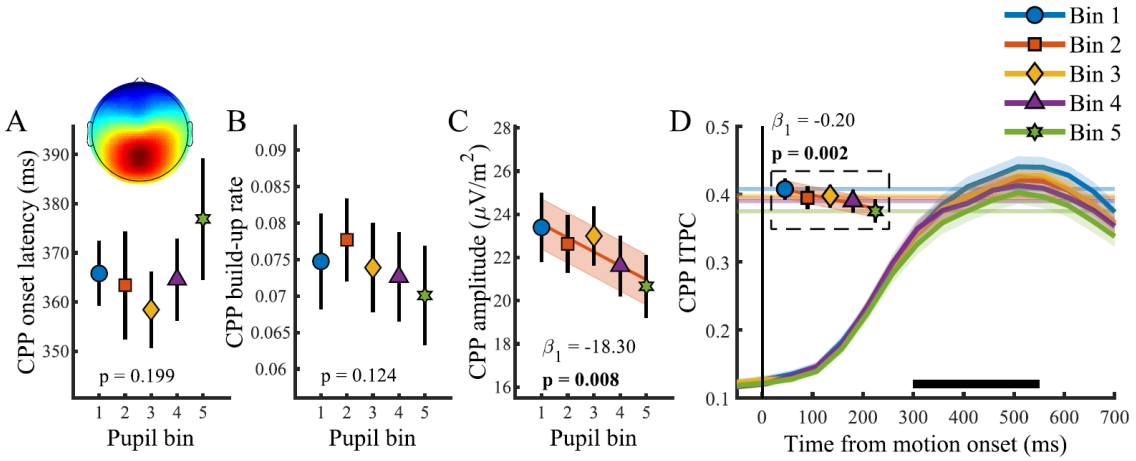


Figure 3.5: Relationship between baseline pupil diameter, that is, tonic arousal, and the CPP. (A) CPP onset latency, (B) build-up rate, (C) amplitude, and (D) ITPC per pupil bin over time. Reprinted from [100].

3.5 The Effect of Ageing on CPP

The majority of what is known about the effects of ageing on decision-making comes from mathematical modelling studies. However, these behavioural studies present limitations, particularly because they cannot fully assess the exact neural processes that are impacted by ageing. Some neurophysiological studies have thus begun to use neural signatures of decision formation and have found consistent findings that are likely to be the cause of several decision making behaviours.

One of these reported findings is that older adults exhibit higher decision boundaries, which suggests that they present a more cautious behaviour, needing a greater amount of evidence to commit to a decision. However, a question that remains unanswered is whether this difference in boundaries is caused by a voluntary preference or a limitation [89].

Another commonly found finding in a wide range of tasks is that older adults present longer non-decision components, such as delays in sensory encoding and/or motion execution [89, 90]. In contrast, ageing effects on the rate of accumulation of evidence, i.e. drift rate, depend much more on the task being performed. This dependency on the task being performed indicates that ageing does not necessarily result in a decline in information processing, but rather impacts specific areas of sensory processing.

Only few studies to date have investigated the effects of ageing on decision signals, such as the CPP, in decision making tasks. The finding that the CPP shares all of the features that have been reported for decision signals makes it possible to develop

neurally informed mathematical models of decision-making. To assess the influence of ageing on neural mechanisms underlying decision formation, McGovern et al. (2018) [90] recruited a group of younger and older subjects to perform a random dot motion task and a gradual contrast change detection task.

With regards to the random dot motion task, and in agreement with previous studies, motion onset prompted an increasing positivity in the ERP from centro-parietal electrodes, in both groups of participants. In terms of behaviour, they found that older adults displayed significant slower RTs. They also observed that the CPP build-up in both groups increased in proportion to evidence strength and that it reached a peak amplitude right before response, which did not vary as a function of evidence strength. However, the rate of CPP build-up was different for both groups, presenting a slower rate of accumulation in the group of older participants. The amplitude at response did not show significant difference between groups, however, the analysis indicated a lower CPP amplitude in the older group, which goes against the consistent finding in literature that older adults exhibit higher decision bounds.

As for the contrast change detection task, older adults and younger adults presented similar average response times. Similarly, the CPP signal was found to be very similar in both groups of participants, with no significant differences in the build-up rate or peak amplitude. Once again, these observations are at odds with previous studies, which indicated that older adults exhibited higher decision boundaries. Therefore, the results of both tasks did not support the consistent finding in literature that older adults set higher decision boundaries, which points to the idea that younger and older adults applied similar decision policies. This does not necessarily mean that the older group does not present a more cautious behaviour, but rather that this could depend on the conditions of the task being performed. In this task, the onset of the stimuli was unpredictable and subjects were told to respond only when sure of their responses, which may have led to more conservative decision policies in both groups. On the other hand, in most previous tasks the onset of the stimulus provides a cue for the initiation of evidence accumulation. Therefore, it could be that older adults set higher decision boundaries when placed under greater time pressure.

Regarding the drift rate, whereas in the random dot motion task the older group exhibited smaller drift rate, in the contrast-change task no such effects were reported. Therefore, drift rate reductions with age are likely to be due to task-specific deficits in sensory encoding. Overall, this study once again confirms the theory that ageing does not result in a decline in decision making processes but rather affects specific

features of sensory input.

Altogether, there are two characteristics associated with age that are typically observed in decision-making. One of them is that older adults set higher decision boundaries, and the other one is that they present longer non-decision components. However, the relationship between ageing, central arousal, performance and neural activity may vary depending on the behavioural paradigm and task demands. In our study, we will be using an auditory task which is not typically used in perceptual decision-making studies, and we will assess how the CPP signal differs between younger and older adults, in order to explore the impact of ageing on the rate of neural evidence accumulation.

4

Methods

This study re-analyzed data that was acquired previously within the scope of a different project. This data was acquired while participants were involved in a cued auditory task, in which the EEG and the pupillogram were recorded. Detailed information on the participants, task design, signal acquisition and artifacts removal can be found in an article by Ribeiro et al. (2019) [44].

Briefly, data from 35 young adults (mean age ± SD = 23 ± 3 years) and 37 older adults (mean age ± SD = 60 ± 5 years) were included in this study. These subjects were required to perform a cued auditory task consisting of two active tasks: the cued simple RT condition, and the cued go/no-go condition. This task design is schematized in Figure 4.1. These active tasks require the subjects to report the detected stimulus by pressing a button as fast as possible. In the simple RT condition, the target stimulus following the cue is always a go-stimulus, therefore the subject needs to respond by pressing the button as soon as he/she detects the stimulus. On the other hand, the go/no-go task can be interpreted as a choice RT task, since it requires not only stimulus detection but also stimulus discrimination between two different stimuli. Once the subject has identified the stimuli, the subject needs to make the decision of whether to press the button or not. Each subject performed a total of 120 trials for each condition. However, error trials were excluded from this study, considering that error trials are trials in which the subjects responded after the cue, failed to respond to the go stimulus, responded too slowly or responded to the no-go stimulus in the go/no condition.

It is worth noting that this task design is different from those that are typically used when studying the evidence accumulation process, since this task is auditory instead of visual.

MATLAB 2019a was used to analyze the artifact-free data, together with the EEGLAB toolbox, version 2020.0 [87]. Statistical analyses were conducted using the LIMO EEG toolbox [101], as well as the IBM SPSS Statistics.

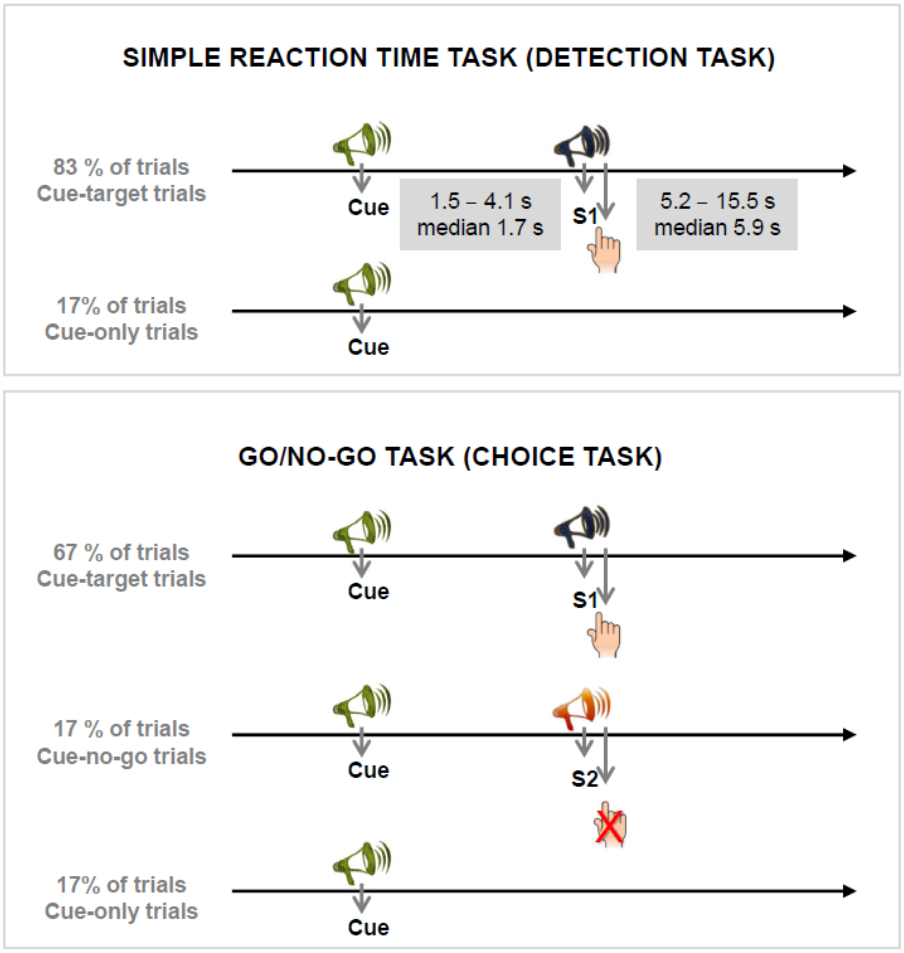


Figure 4.1: Task design. Reprinted from [44].

4.1 Pupillometry Acquisition and Analysis

The pupil diameter of the right eye was measured by an infrared eye-tracker (iView X Hi-Speed 1250 system from SMI) with a sampling rate of 240 Hz. When acquiring the pupil data, triggers were generated at the onset of the cue, at the onset of the stimulus and at the time of button press, for each trial, which allowed us to segment pupil epochs locked to these different time points.

To start off the analysis, pupil data, from which the blink artifacts had already been linearly interpolated, were imported into EEGLAB, where data from all runs were merged for each subject. Then, pupil diameter response was normalized by dividing by the pupil diameter by its mean, according to the following formula: pupil diameter/mean(pupil diameter). Lastly, this signal was cut into epochs locked to cue onset from -1000 ms until 6000 ms, and average baseline activity (set from -500 ms to cue onset) was removed for each trial.

The baseline pupil diameter was defined as the mean pupil diameter during the 500 ms preceding cue onset on each trial.

To investigate the relationship between pupil-linked arousal and behavioural performance during decision-making, particularly the reaction time (RT), we binned our RT data according to either the baseline pupil diameter or the preparatory pupil diameter into three equally sized bins. The preparatory pupil was extracted from the cue-locked pupil waveform, as the average value on the window from 0 ms to 1500 ms. To do the statistical analysis of these RT data we used IBM SPSS Statistics and we performed a repeated measures ANOVA, for which the within-subject factors were the tertile and the task, and the between-subject factor was the age group. In the event of a significant task $\times$ tertile interaction, we would do a repeated measures ANOVA for each task, for which the within-subject factor was the tertile and the between-subject factor was the age group.

A repeated measures ANOVA with a between-subject factor is also called a mixed ANOVA. If there are two within-subject factors and one between-subject factor, as in our study, this is called a three-factor mixed ANOVA. On the other hand, if there is one within-subject factor and one between-subject factor, as when assessing a significant task $\times$ tertile interaction in our study, it is called a two-way mixed ANOVA. These tests are used when the subjects have been assigned into two separate groups (in this case, based on age). These groups form the between-subject factor. The primary goal of a mixed ANOVA is to understand if there is an interaction between these two or three factors on the dependent variable. By using this statistical model, we were able to investigate if tonic arousal (estimated from pupil size at baseline) and phasic arousal (estimated from the pupillary response evoked by the cue stimulus) are predictive of RT, and how does this relation varies across age group, for each task.

4.2 EEG Acquisition and Analysis

Regarding the acquisition, the EEG signal was recorded using a 64-channel Neuroscan system with scalp electrodes placed according to the International 10–20 electrode placement standard, with an acquisition rate of 500 Hz. Vertical and horizontal electrooculograms were recorded to monitor eye movements and blinks. Artifacts were corrected, using independent component analysis (ICA) and through visual inspection, so as to eliminate non-brain sources such as eye blinks, muscular artefacts, single-channel artefacts, lateral eye movements, and high frequency line

noise.

In order to study the neural correlates of the evidence accumulation process, and in line with van Kempen et al. (2019) [100], the CPP was defined as the signal at the electrode Pz. According to the 10-20 electrode placement standard, the letter P stands for Parietal lobe and the letter z refers to an electrode placed on the midline of the skull. This international system of EEG placement can be visualized in Figure 4.2.

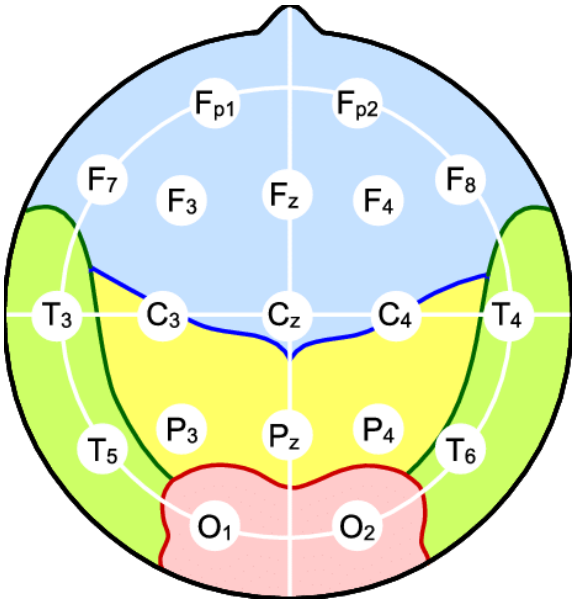


Figure 4.2: 10-20 system of electrode placement. Reprinted from [102].

Firstly, data from all runs were merged for each subject. Then, to obtain the response-locked waveform of the CPP, epochs were extracted from -1000 to 1000 ms around response onset and baselined with respect to -100 to 0 ms before target onset. The target-locked waveform was also obtained, by extracting the epochs from -1000 to 2300 ms around target onset.

To examine whether the CPP amplitude could predict RT on individual trials, we binned our CPP data according to the RT into three equally sized bins. The same procedure was applied to examine the relationship between the CPP amplitude and the pupil dynamics (preparatory pupil response and baseline pupil diameter). We first performed these analyses using the response-locked waveform of the CPP. The CPP build-up rate was computed as the slope of a straight line fitted to this signal in the window from -150 ms to 0 ms before response. Lastly, statistical analyses were performed to find out if this slope was correlated with either the RT, the preparatory pupil response or the baseline pupil diameter. The statistical analyses

were conducted using IBM SPSS and by doing a repeated measures ANOVA, for which the within-subject factors were the tertile and the task, and the between-subject factor was the age group. We then repeated these analyses by aligning the CPP to the target and calculating its build-up rate in the window between 100 and 250 ms post-target. The following figures show a graphic representation of this calculation, in which the red dashed line represents the linear regression line and the green plot represents the ERP at electrode Pz.

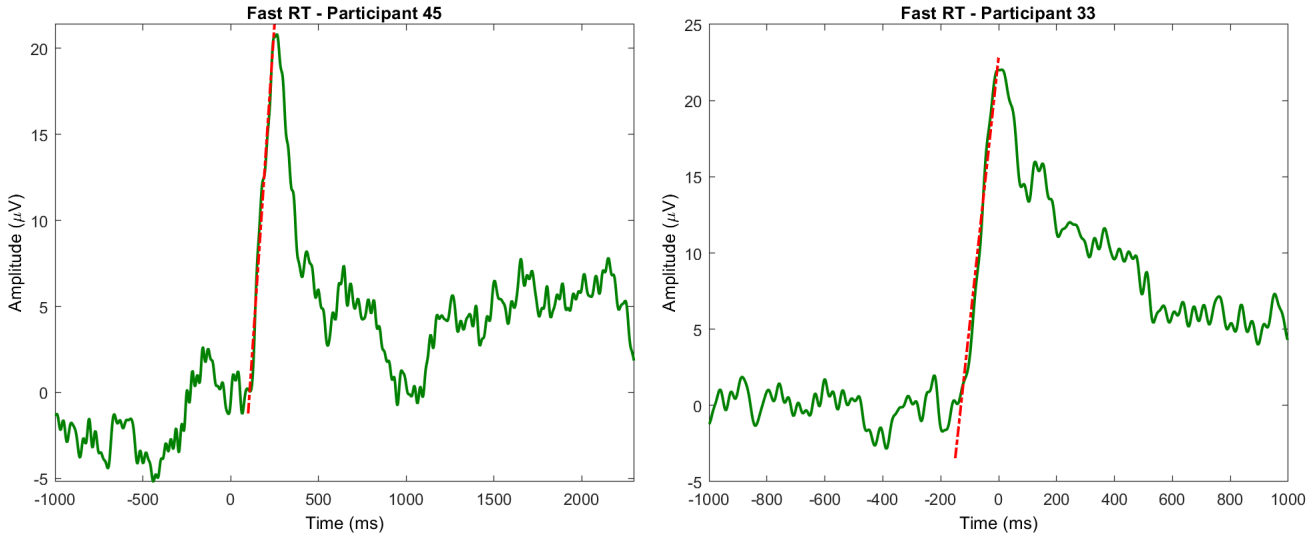


Figure 4.3: Graphic representation of the linear regression performed, using the target-locked waveform of the CPP (left) and the response-locked waveform of the CPP (right), in order to calculate the build-up rate of the CPP.

We then used the LIMO toolbox to perform time point-by-time point correlation analyses between the ERP at the electrode Pz and three continuous variables: the RT, the preparatory pupil response and the baseline pupil.

The LIMO EEG toolbox [101] for Matlab stands for hierarchical LInear MOdelling of EEG data and it uses a massive univariate approach, which means that it allows analysing effects at all electrodes and all time points. This toolbox is based on a hierarchical linear model, being that the within-subject variance is considered in the first level. In the first level, a general linear model (GLM) is used to model all trials at all time points for each subject. In this level, trials are seen as independent observations from the population which is the subject. The GLM can take categorical as well as continuous variables. The end result of this level are beta parameters for each subject, which are the output of the GLM. These estimated beta parameters [subjects × electrodes × time-frames × regressors] are then integrated across sub-

jects in the second level, and robust statistics are performed on them to test for significance across subjects. These statistics depend on the research question, but the statistical tests available in the LIMO EEG GUI are the following: one sample t-test, paired t-test, two samples t-test, regressions, one way ANOVA, one way ANCOVA and repeated measures ANOVA. An overview of this hierarchical model is visually represented in Figure 4.4.

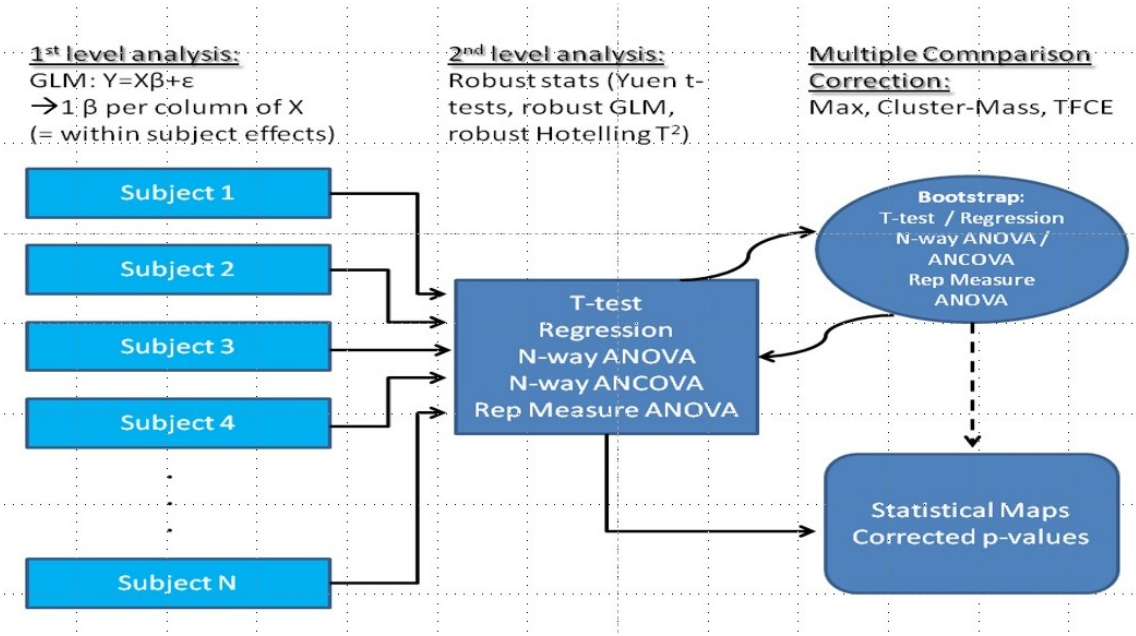


Figure 4.4: Hierarchical linear modelling approach used in LIMO EEG. Figure from *https://github.com/LIMO-EEG-Toolbox/limo_tools/wiki*.

In our study, the model used in the first level analysis included a categorical variable, which makes the distinction between the simple RT task trials and the go/no-go task trials, and a continuous variable, which is the variable to which we want to correlate the CPP with (that is, the RT, the preparatory pupil or the baseline pupil). In the first level, a design matrix is plotted for each subject, using the *limo_design_matrix.m* function. This design matrix contains information about the variables (i.e., predictors) we want to use in the second level. An example of the design matrix can be seen in Figure 4.5.

This model was performed six times, because we used three continuous variables and two waveforms of the CPP. In the target-locked analyses, parameters were computed from 0 ms to 800 ms after target onset. As for the response-locked analyses, we used response-locked epochs baselined with respect to -100 ms before target, and parameters were computed from -500 ms to 100 ms after button press.

By doing this using the *limo_eeg.m* function, we obtained the beta parameter estimates for each participant. We plotted these beta parameters for each predictor, to get an idea of where we were going to find significant differences in terms of group effect.

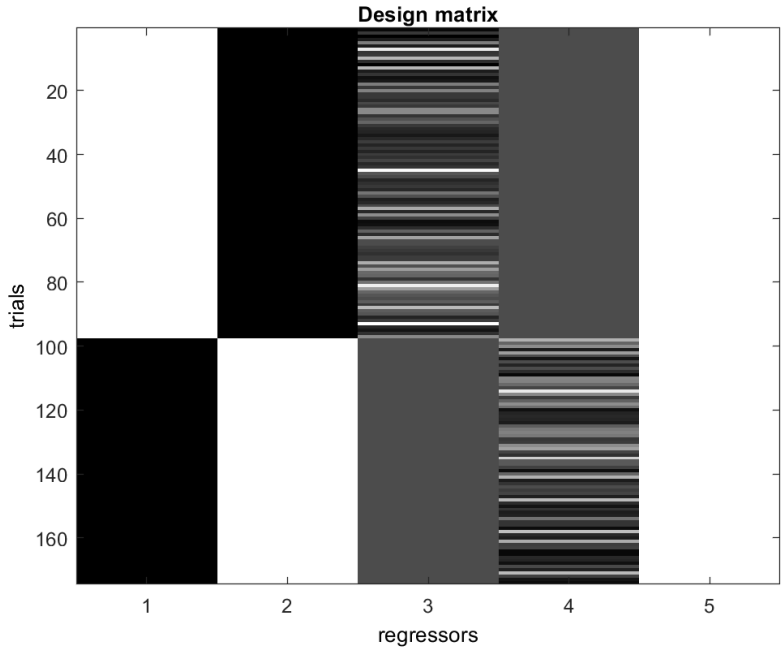


Figure 4.5: Example of the Design Matrix. The first two predictors are categorical and they represent task type, with the first one representing the simple RT task and the second one representing the go/no-go task. The third and fourth predictors are continuous and they represent one of the continuous variables (RT, preparatory pupil, baseline pupil) for each task. The last column is a constant term.

Then, the second level analysis takes those parameter estimates and performs statistics on them, using the *limo_random_robust* function. In our case, we took parameter 3 and 4 and we used a repeated measures ANOVA, with task type as a within-subject factor and age group as a between-subject factor. Therefore, the model had 2 categorical predictors, task type and group, and an interaction term between task conditions and group. We also did one-sample t-tests for each group and each task. The end result of both of these statistical models is a variable called *mask*, which corresponds to the region of our data where there is a significant correlation between the variables being analysed after controlling for multiple comparisons using a spatio-temporal clustering method.

The Contigent Negative Variation (CNV) is another slow potential that shares some similarities with the CPP [103]. This potential is observed during the period between

the cue and the target stimulus, and usually measured at a frontal electrode, the FCz, and it is known to be modulated by different levels of attention, task difficulty and motivation. It is also implicated in an accumulation process, however a temporal accumulation, instead of evidence accumulation. Besides, the CNV does not always increase until response latency. For these reasons, it is unlikely that the CPP and the CNV reflect the same decision signal. We examined if there was an effect of the CNV during the preparatory period before target onset in the build-up rate of the CPP observed after target onset. For this, we measured the CNV at the frontocentral electrode FCz in the window from 1000 ms to 1500 ms using the cue-locked waveform. Then, we binned the CPP into tertiles, according to the sorted CNV potential. Lastly, the build-up of the CPP was computed in the window from -150 ms to 0 ms using the response-locked waveform. Once again, to find out if this CPP build-up is correlated with the preparatory ERP at the fronto-central electrode, statistical analyses were conducted using IBM SPSS and by doing a repeated measures ANOVA, for which the within-subject factors were the tertile and the task, and the between-subject factor was the age group.

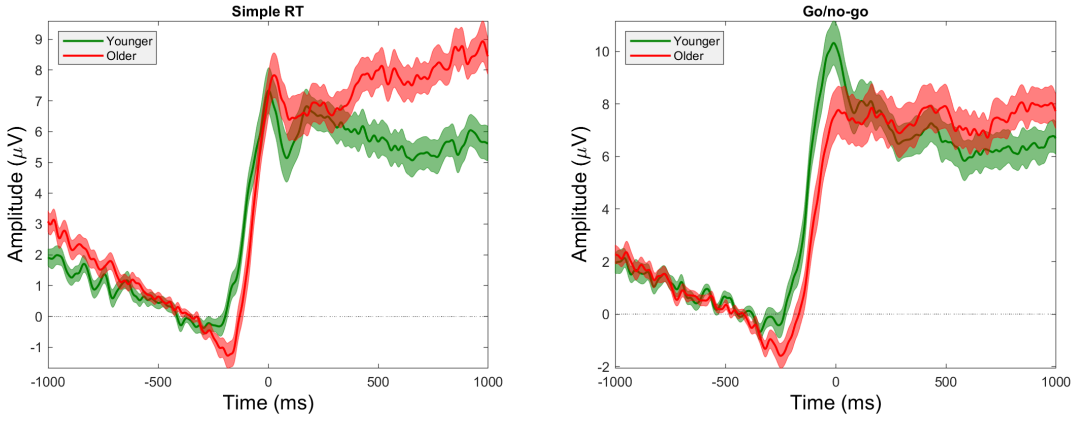
Lastly, we also assessed if there was an effect of the CNV on the RT. In order to do this, we binned the RT into tertiles, according to the sorted CNV potential. Then, we did a repeated measures ANOVA, for which the within-subject factors were the tertile and the task, and the between-subject factor was the age group.

5

Results and Discussion

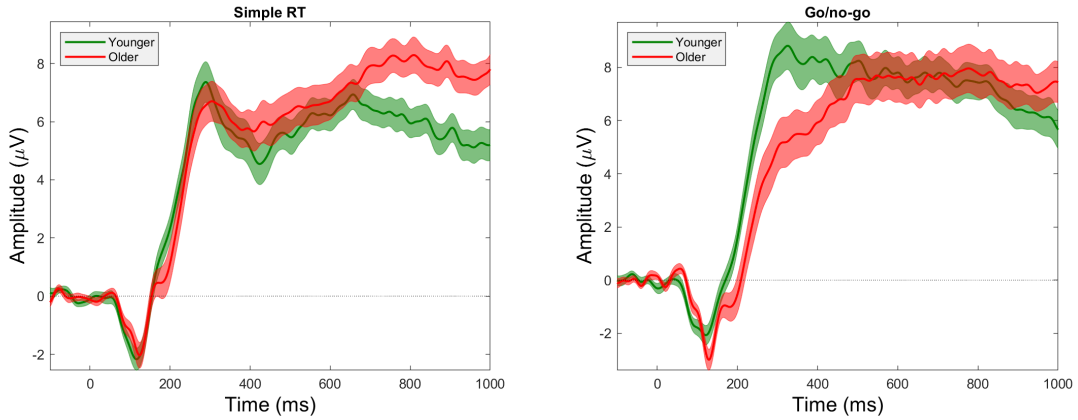
In this chapter, all the results of the aforementioned procedures are presented and discussed.

To measure the impact of ageing on neural evidence accumulation processes and to investigate whether there is a relationship between the behavioural and neural correlations of decision-making with pupil-linked arousal, we used existing data from a decision-making auditory task. In agreement with previous research, the target onset elicited an increasing positivity in the ERP at the Pz electrode in both age groups (younger and older) and both tasks (simple RT and go/no-go), which can be seen in Figures 5.1 and 5.2. Before this increasing positivity, and differently to previous studies found in literature, there is a negative peak, whose origin is unknown.



(a) **(b)**

Figure 5.1: Response-locked CPP in the a) simple RT condition; b) go/no-go condition. As expected, the build-up of the CPP reached a peak at response latency.



(a) **(b)**

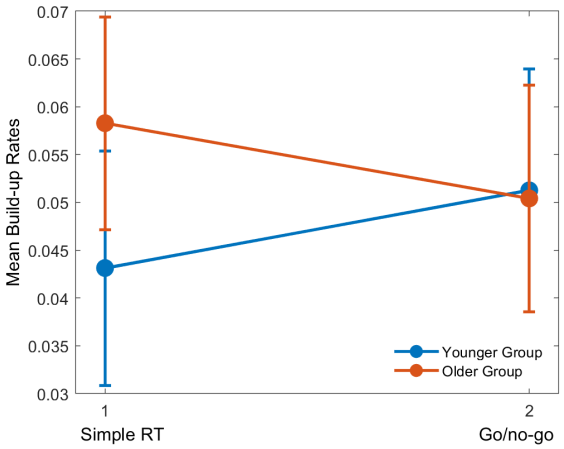
Figure 5.2: Target-locked CPP in the a) simple RT condition; b) go/no-go condition.

It has been shown that the CPP presents the key characteristics of accumulation that are often described in the sequential sampling models of perceptual decision-making. For instance, its build-up rate increases with evidence strength, it covaries with RT and it peaks immediately before response execution. In the present study, we made use of these evidence accumulation properties to investigate the effect of ageing and the effect of arousal on the build-up rate of the CPP.

We started by performing the statistical comparison of the response-locked CPP build-up rate of both groups and tasks, by doing a mixed ANOVA with the task as the within-subject factor and the group as the between-subject factor. The results showed no significant effect of task [$F_{(1,70)} = 0.002$, $p = 0.969$] or group [$F_{(1,70)} = 0.865$, $p = 0.355$], but rather they showed a significant Task $\times$ Group [$F_{(1,70)} = 6.045$, $p = 0.016$].

This significant Task $\times$ Group interaction results from the fact that the build-up rates are different between groups in the simple RT task, but not in the go/no-go task, as can be seen in Figure 5.3. This observation is interesting because in the go/no-go task the older group responds more slowly than younger subjects, despite their build-up rates being the same, which suggests that the non-decision time components are higher in the older subjects, which is according to the literature. In the simple RT task, the older group is able to respond as quickly as the younger group. This means that the older subjects compensate having slower non-decision time components by presenting a greater speed of accumulation of evidence, which could reflect a greater effort on their part. To further assess this, we performed an independent samples t-test for each task. We found that in the simple RT task, the

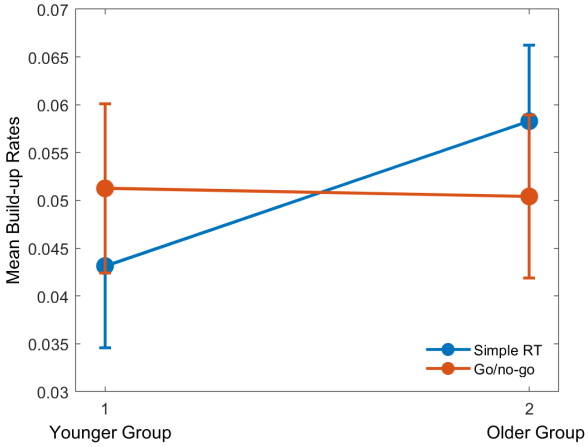
effect of group is almost but not quite significant [$F_{(1,70)} = 0.313$, $p = 0.067$]. As expected, there was no effect of group in the go/no-go task [$F_{(1,70)} = 0.330$, $p = 0.922$].



(a)

Figure 5.3: Mean build-up rates of the response-locked CPP of each task, separated by group. Error bars represent 95% confidence intervals.

By plotting the graph differently, in a way that we can assess the Group × Task interaction (see Figure 5.4), we can see that the modulation of the build-up rate is different in both groups. The older group reduces their build-up rate from the simple RT task to the go/no-go task, while the younger group increases it. We assessed this difference by doing a repeated measures ANOVA for each group, with the task as the within-subject factor. Even though this task difference is visible in the graph, the effect of task was not significant for any of the groups [younger group: $F_{(1,70)} = 3.168$, $p = 0.084$; older group: $F_{(1,70)} = 2.964$, $p = 0.094$].



(a)

Figure 5.4: Mean build-up rates of the response-locked CPP of each group, separated by task. Error bars represent 95% confidence intervals.

5.1 Relation between Task Performance and Arousal

Here, we started by visually representing the effect of the baseline pupil on the pupil response time course, for each task and each age group, in order to verify that our pupil dynamics are behaving similarly to what has been described in previous studies. To do this, we divided the pupil response in tertiles according to the sorted baseline pupil diameter. In Figure 5.5 we have the result of this same analysis, taken from an article by van Kempen et al. (2019) [100], to showcase how this pupil time course should change with the baseline pupil. Our results are presented in Figure 5.6, where Bin 1 represents the trials with the smallest pupil baseline values, Bin 2 represents the trials with intermediate pupil baseline values, and Bin 3 represents the trials with the largest pupil baseline values. As expected, and according to the literature, pupil diameter dilations to the cue were larger for small than for large baseline pupil trials.

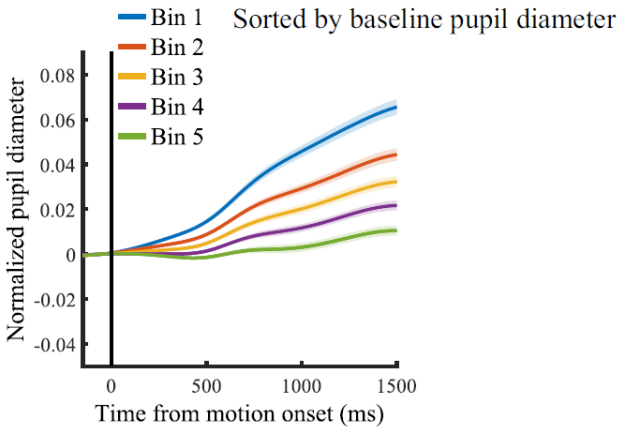
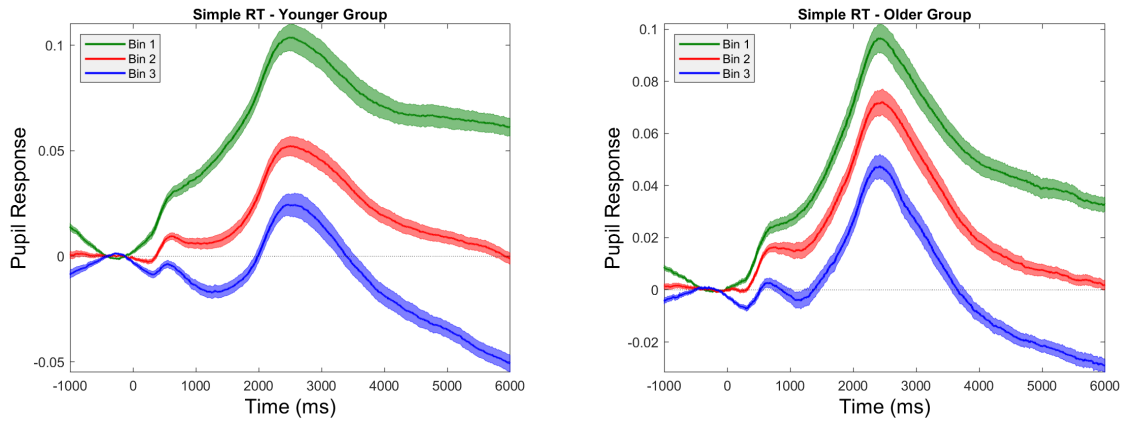
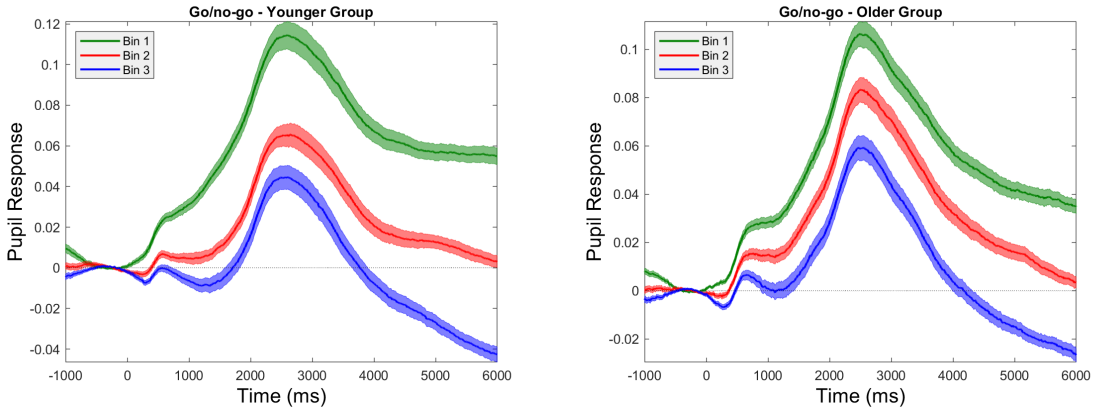


Figure 5.5: Pupil diameter time course sorted by baseline pupil diameter. Reprinted from [100].



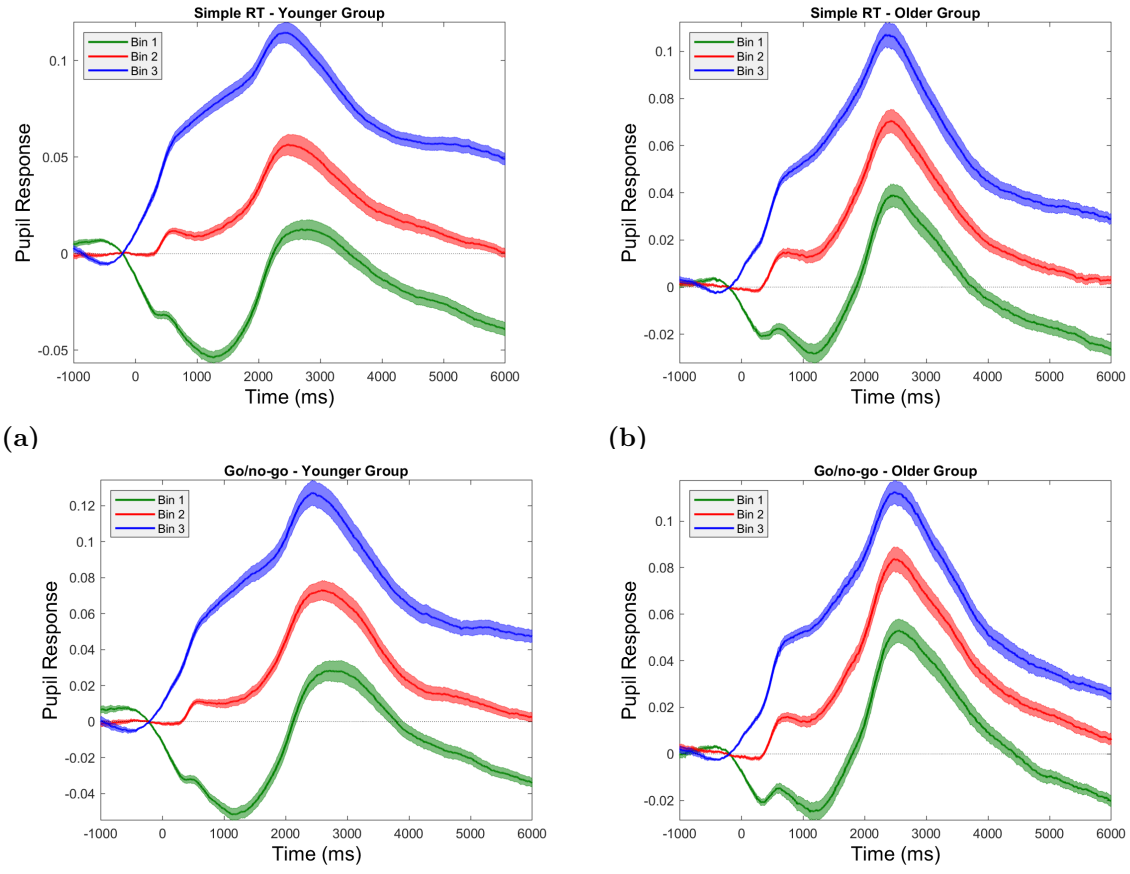
(a) **(b)**



(c) **(d)**

Figure 5.6: Effect of the baseline pupil diameter on the cue-locked pupil response in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.

We also represented the time course of the pupil diameter in Figure 5.7, for each group and each task, sorted by the pupil diameter response itself, which behaved just as expected.



(a) **(b)**

(c) **(d)**

Figure 5.7: (Caption next page.)

Figure 5.7: (Previous page.) Pupil diameter time course sorted by the pupil diameter response in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.

Before proceeding further, we will go over some of the behavioural results found in the article by Ribeiro et al. (2019) [44], particularly the ones related with RT since all of our analyses include only the correct trials. By analysing the RT, the authors found a significant effect of task. By exploring this effect, it was found that correct responses in the go/no-go task were significantly slower than in the simple RT task. Besides, there was also a significant Task × Group interaction, which was present because the difference in reaction times between tasks was higher in the older subjects than in the younger subjects. Indeed, older subjects, in comparison with their younger counterparts, responded on average faster, in the simple RT task than in the go/no-go task. This can be better understood by looking at Figure 5.8. Lastly, there was no effect of group.

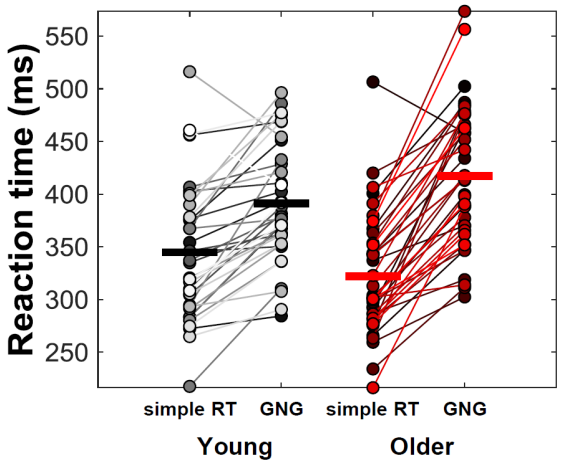


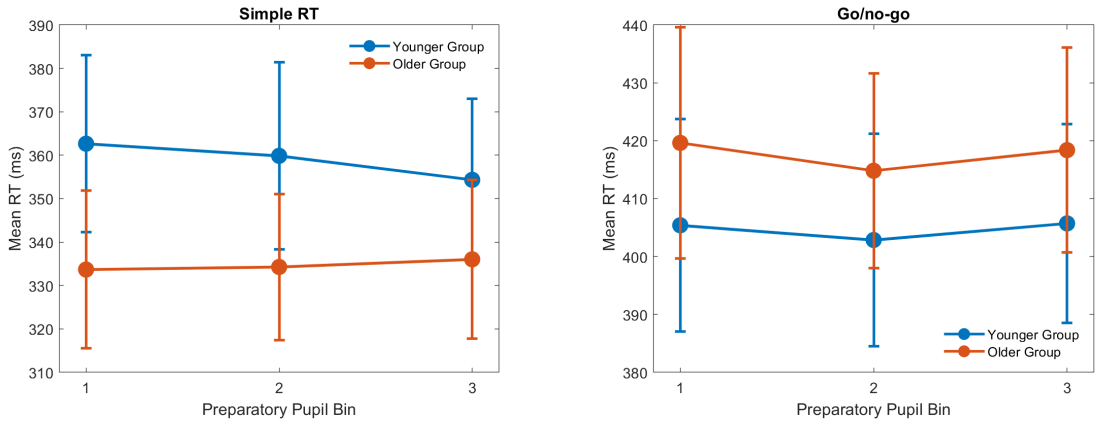
Figure 5.8: RTs of both groups of subjects, for the simple RT and the go/no-go task. Reprinted from [44].

We decided to bin the RT according to the sorted pupil diameter response, to investigate if phasic arousal was predictive of behavioural performance. We then performed a mixed ANOVA with both the task and tertile as the within-subject factors, and the group as the between-subject factor.

The results of this test revealed a significant effect of task [$F_{(1,70)} = 164.361$, $p < 0.001$] and a significant Task × Group interaction [$F_{(1,70)} = 13.774$, $p < 0.001$]. There was not a significant effect of tertile [$F_{(2,140)} = .732$, $p = 0.483$], tertile × group interaction [$F_{(2,140)} = .740$, $p = 0.479$], task × tertile interaction [$F_{(2,140)} =$

1.005, $p = 0.369$], 3-way task × tertile × interaction [$F_{(2,140)} = 1.449$, $p = 0.238$] or group [$F_{(1,70)} = .244$, $p = 0.623$]. Overall, this indicates that there is not a correlation between the preparatory pupil response and the RT, for any age group or task. Besides, the Task × Group interaction results from the differences in RT found between tasks and groups, already mentioned when going over the behavioural results found in the article by Ribeiro et al. (2019) [44].

These effects can be better understood when plotting the means of the RTs of each bin, for each age group and task (see Figure 5.9).

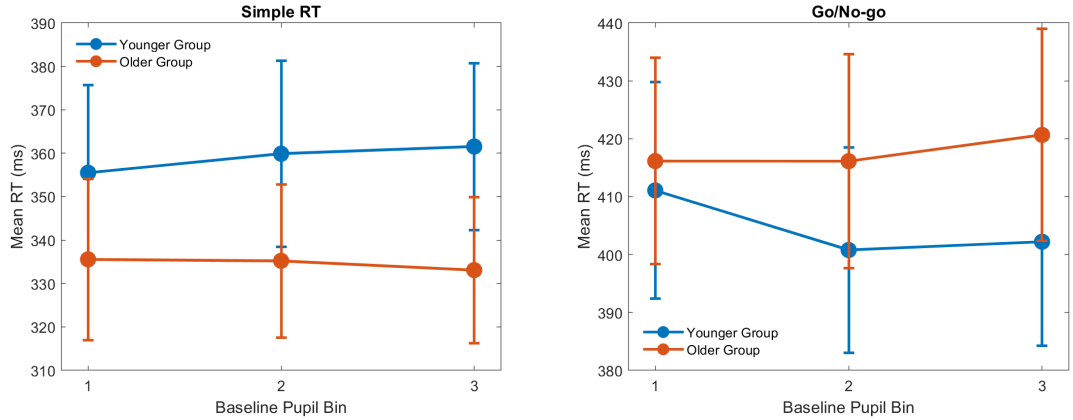


(a) **(b)**

Figure 5.9: Mean RTs sorted by the cue-locked pupil response in the preparatory period from 0 ms to 1500 ms, in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

We also binned the RT according to the sorted baseline pupil diameter, to study the effect of tonic arousal modulations on RT. Regarding the relation between tonic arousal and RT, the results of the mixed ANOVA with two-within subject factors (task and tertile) and one between-subject factor (age group) showed that there is a significant effect of task [$F_{(1,70)} = 164.344$, $p < 0.001$] and a significant Task × Group interaction [$F_{(1,70)} = 13.8$, $p < 0.001$]. Once again, and looking at Figure 5.10, this is due to the behavioural differences found between tasks and groups. We also found a significant Task × Tertile × Group interaction [$F_{(2,140)} = 4.444$, $p = .013$], which indicates that the effect of tertile depends on the task and on the group; specifically, we can see in Figure 5.10, that a larger baseline pupil is predictive of a faster response, but only in the younger group and in the go/no-go task. Similarly to what was shown when binning the RT according to the pupil response, there were no significant effects of tertile [$F_{(2,140)} = .329$, $p = .720$], tertile × group [$F_{(2,140)} = .258$, $p = .773$] or task × tertile [$F_{(2,140)} = 1.836$, $p = .163$], meaning that we did

not find any significant correlation between the baseline pupil and the RT, for any age group or task. Lastly, there was not a significant effect of group [$F_{(1,70)} = .246$, $p = .621$].



(a) **(b)**

Figure 5.10: Mean RTs sorted by the baseline pupil in the preparatory period from 0 ms to 1500 ms, cue-locked, in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

Now that we concluded that both tonic and phasic arousal do not predict our performance data, we will concentrate on the relationship between these measures (RT and both pupil dynamics) and the neural correlate of the evidence accumulation process, the CPP.

5.2 Relation between CPP and Reaction Time

One measure of the CPP that reflects the decision making process is that its slope, i.e. its build-up rate, scales with RT. In this section, we study how this relationship varies with age group and task. First, we visually represent how the time course of the CPP amplitude changes with RT, for both tasks and groups (see Figure 5.11).

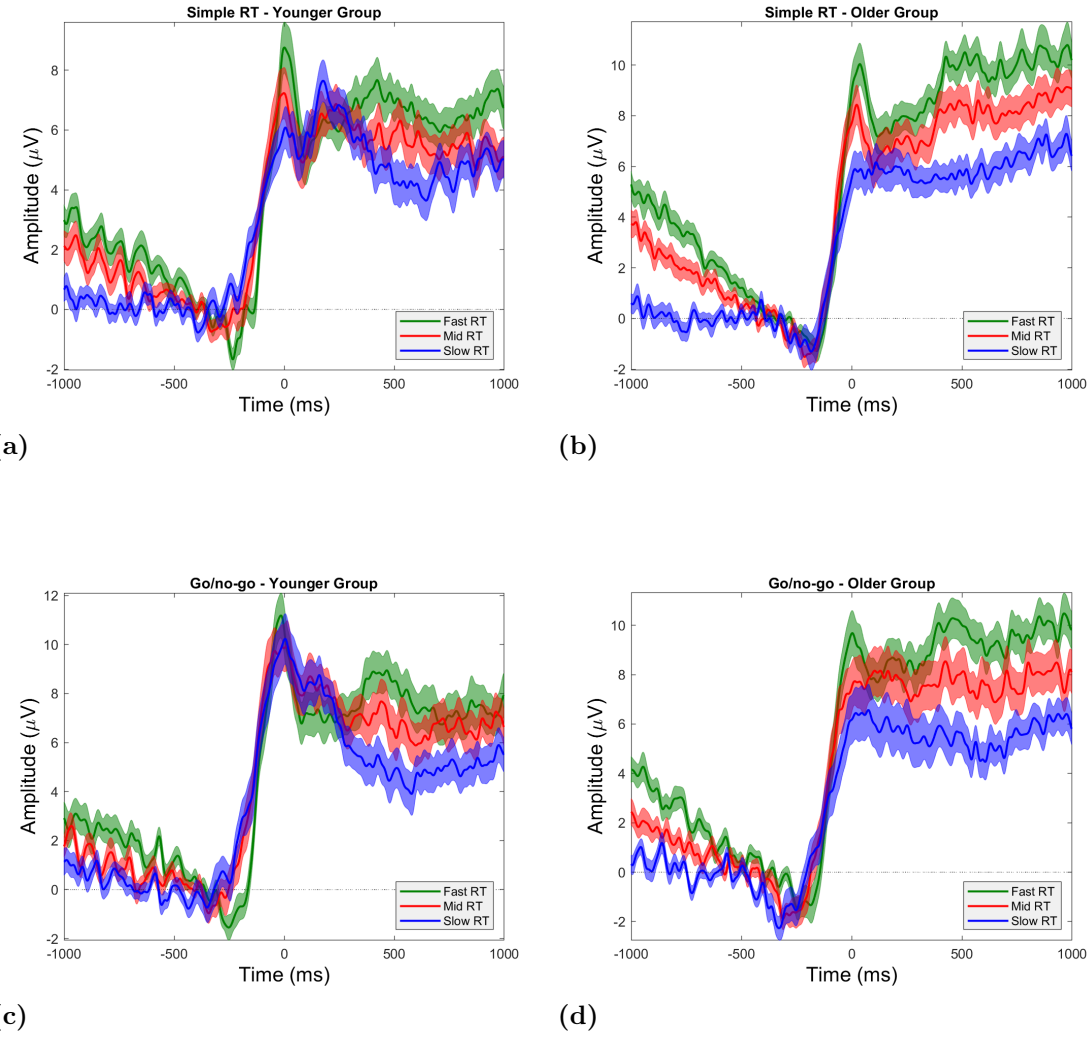
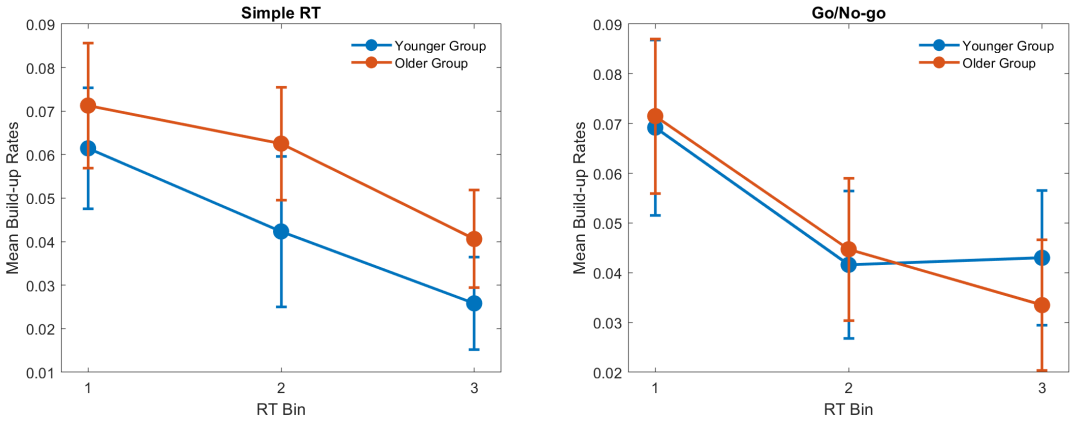


Figure 5.11: The response-locked CPP in relation to the RT, in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.

We performed a mixed ANOVA with two within-subject factors, the tertile and the task, and one between-subject factor, the age group. The results of this test revealed a significant Task × Group interaction [$F_{(1,70)} = 6.277$, $p = 0.015$], a significant effect of Tertile [$F_{(2,140)} = .078$, $p < 0.001$], and a significant Task × Tertile interaction [$F_{(2,140)} = 3.917$, $p = 0.022$]. There were no significant effects of task [$F_{(1,70)} = .001$, $p = 0.978$], tertile × group interaction [$F_{(2,140)} = .795$, $p = 0.454$], three-way interaction task × tertiles × group [$F_{(2,140)} = 1.090$, $p = 0.339$], or a group effect [$F_{(1,70)} = 0.775$, $p = 0.382$]. The effect of tertile indicates that there is a correlation between the CPP build-up rate and the RT, as expected. There was no tertile × group interaction, meaning that this effect is approximately the same for both groups, but there was a Tertile × Task interaction, which means that this

modulation is stronger in one of the tasks. Notably, there is no effect of group, meaning that on average the build-up rate is the same in young and older adults. However, the significant Task × Group interaction is important because it means that the difference in build-up rates between groups depends on the task. In other words, although there is no significant group difference, there is a difference in the way that the build-up rate varies with the task in one group and the other, as we saw in the beginning of this chapter.

To assess the Tertile × Task interaction, we performed a mixed ANOVA for each task, in which the within-subject factor was the tertile, and the between-subject factor was the age group. These statistical analyses revealed that the CPP build-up rate correlates with RT, in both the simple RT task [$F_{(2,140)} = 33.220$, $p < 0.001$] and the go/no-go task [$F_{(2,140)} = 23.300$, $p < 0.001$]. It is clear, by looking at Figure 5.12, that in faster trials the CPP build-up rate is steeper, and it seems that this modulation is stronger in the simple RT task. Lastly, there was not a significant effect of group [simple RT: $F_{(1,70)} = 3.341$, $p = 0.072$; go/no-go: $F_{(1,70)} = 0.025$, $p = 0.874$] or a significant effect of the group × tertile interaction, in any of the tasks [simple RT: $F_{(2,140)} = 0.806$, $p = 0.449$; go/no-go: $F_{(2,140)} = 0.975$, $p = 0.380$].

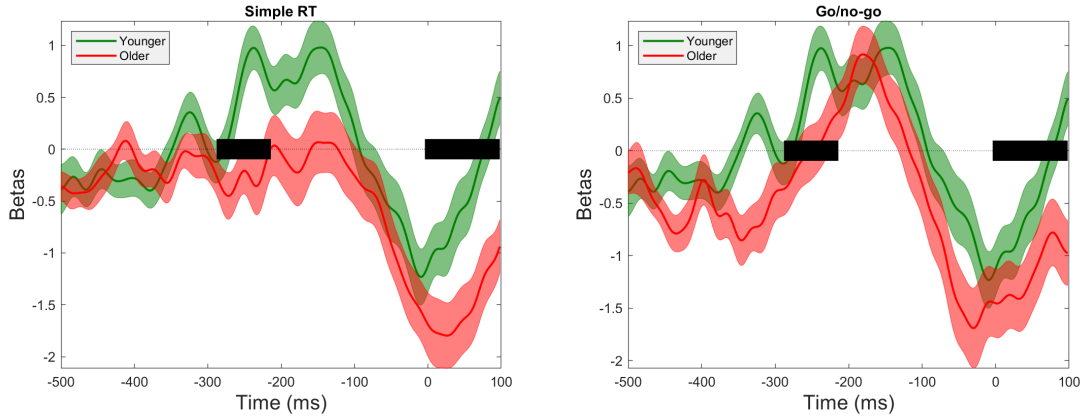


(a) **(b)**

Figure 5.12: Mean build-up rates of the response-locked CPP sorted by the RT, for both age groups in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

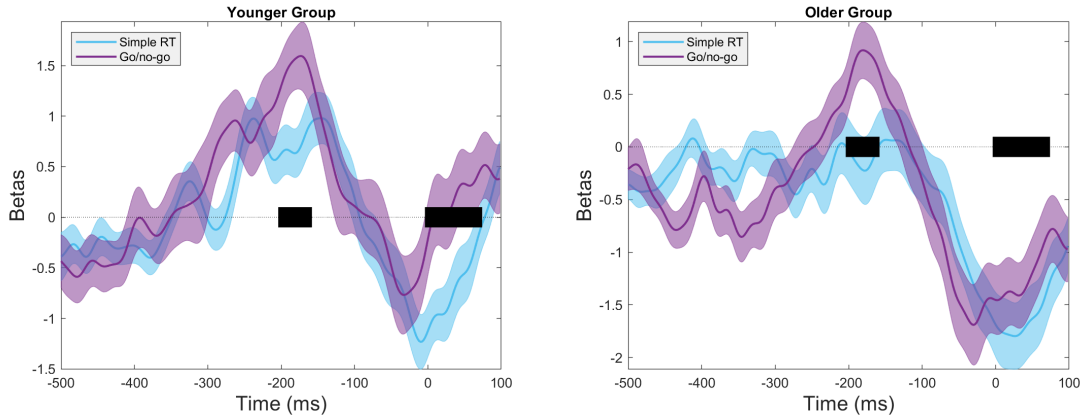
We also performed time point-by-time point correlation analyses between the response-locked CPP and the RT. Taking into account the previous analysis, it is expected that the CPP and the RT are correlated in the CPP build-up time window, i.e., from -150 ms to 0 ms before response. Besides, we did not find a significant effect of group or task in this time window, which we expect to confirm in this new analysis.

In the first level of the LIMO toolbox, we obtained the beta parameters for each participant and for each time point. We plotted their mean, and by looking at Figure 5.13 and Figure 5.14, we can see that the time points where the betas are different than zero, are where we will possibly have significant effects of group and task, respectively.



(a) **(b)**

Figure 5.13: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the RT in a) the simple RT task, and b) the go/no-go task. A significant effect of group is represented by the horizontal black bars.



(a) **(b)**

Figure 5.14: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the RT in a) younger subjects, and b) older subjects. A significant effect of task is represented by the horizontal black bars.

After obtaining the parameters from the single participants, the model performed a repeated-measures ANOVA with task condition as the within-subject factor and

age group as the between-subject factor. These time point-by-time point statistical comparisons revealed differences across task conditions and differences across groups, but no Task × Group interactions. The time windows presenting significant task effects at the group level are represented in Figure 5.14 and the time windows presenting significant group effects at the task level are represented in Figure 5.13, by horizontal black bars. These time windows are also numerically presented in Table 5.1. To better understand the significant effect of group found in this analysis, we also calculated these time windows using the target-locked waveform, which are present in Table 5.2. These findings indicate a significant effect of group between the CPP and the RT at response latency, and even after this moment.

Table 5.1: Time windows in which there is a significant effect of group and task, using the response-locked waveform.

Repeated Measures ANOVA	Effect of Group	Effect of Task
	[-288, -214], [-4, 98] ms	[-204, -158], [-4, 74] ms

Table 5.2: Time windows in which there is a significant effect of group and task, using the target-locked waveform.

Repeated Measures ANOVA	Effect of Group
	[288, 800] ms

We then did one sample t-tests to find out the time windows in which there is a correlation between the amplitude at electrode Pz and the RT, for each group and task. These time windows are presented in Table 5.3.

Table 5.3: Time windows in which there is a significant correlation between the response-locked CPP and the RT, using the response-locked waveform.

one sample t-test	Simple RT	Go/No-Go
Younger	[-194, -114], [-32, 66] ms	[-238, -134] ms
Older	[-58, 98] ms	[-472, -410], [-74, 98] ms

In the previous analyses, we divided the RT data in tertiles and assessed if there was a group effect in the way that RT correlated with the CPP build-up. We did not observe any group effect in the time window where we calculated its build-up, that is, from -150 ms to 0 ms before response. The current analysis confirms those results, because we did not find a significant effect of group in that same time window.

The CPP build-up rate should be informative of a person's drift rate, that is, the person's rate of evidence accumulation. Overall, we can conclude that the build-up rate of the CPP is predictive of RT, meaning that faster accumulation of evidence is associated with faster RTs. In addition, we once again confirmed the significant Group × Task interaction, which shows that older adults modulate their rate of evidence accumulation according to the difficulty of the task differently from young adults.

5.3 Relation between CPP and Arousal

5.3.1 Effect of the Pupil Preparatory Response

Here we investigated the relationship between the preparatory pupil diameter response and the build-up rate of the CPP. Figure 5.15 exhibits the time course of the CPP amplitude, binned in relation to the preparatory pupil response.

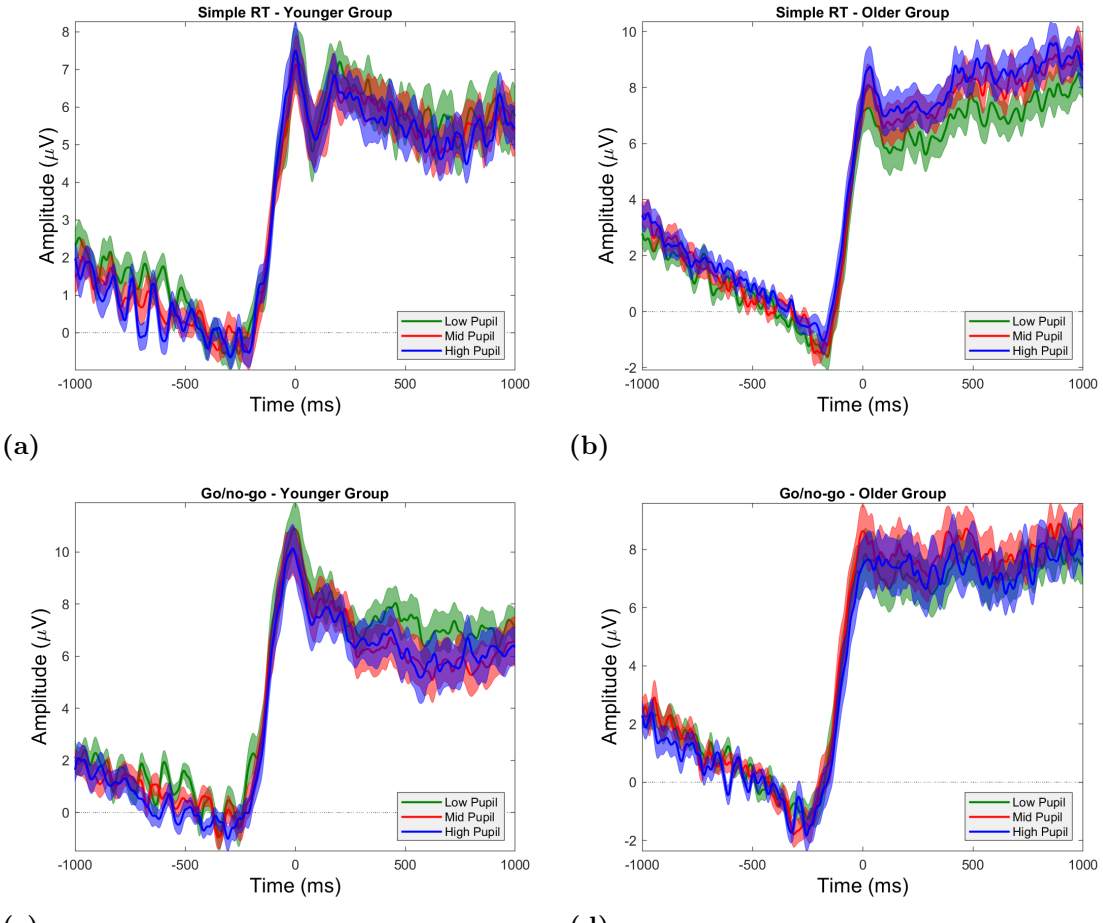
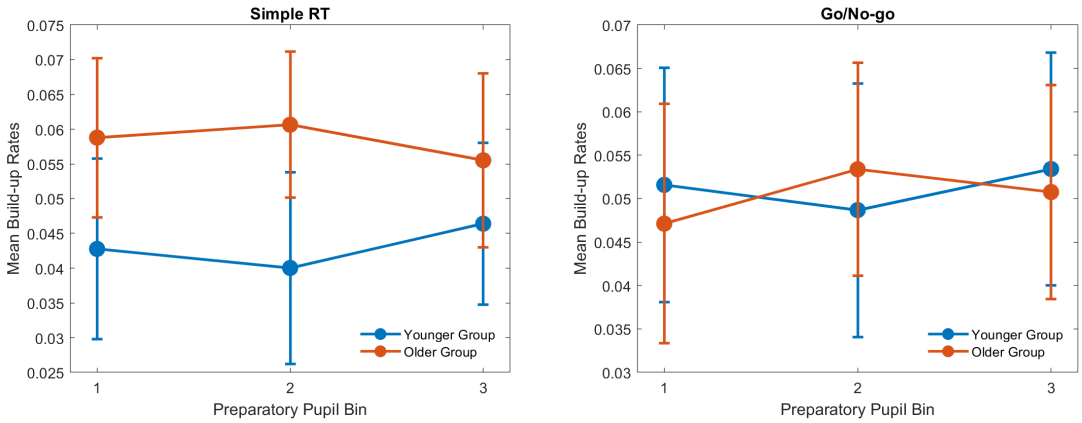


Figure 5.15: The response-locked CPP in relation to the preparatory pupil response, in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.

We performed a mixed ANOVA with two within-subject factors, the tertile and the task, and one between-subject factor, the age group. The means of the build-up rates of each bin are plotted in Figure 5.20. The results of this test revealed a significant Tertile × Group interaction [$F_{(2,140)} = 3.325$, $p = 0.039$] and a significant Task × Group interaction [$F_{(1,70)} = 6.121$, $p = 0.016$]. On the other hand, the test revealed no significant effects of tertile [$F_{(2,140)} = .299$, $p = 0.742$], task [$F_{(1,70)} = .002$, $p = 0.967$], tertile × task interaction [$F_{(2,140)} = .282$, $p = 0.754$], three-way interaction task × tertiles × group [$F_{(2,140)} = 0.716$, $p = 0.490$], or a group effect [$F_{(1,70)} = .881$, $p = 0.351$].

The non-existence of a significant effect of tertile indicates that the CPP build-up did not correlate with the preparatory pupil response. To assess the significant Tertile × Group interaction, we performed a mixed ANOVA for each group, with the tertile and the task as within-subject factors, however we did not find significant effects of tertile for any of the groups [younger group: $F_{(2,140)} = 1.952$, $p = 0.150$; older group: $F_{(2,140)} = 1.625$, $p = 0.204$]. However, by looking at Figure 5.16, we can see that the slope in the older group is highest for the intermediate pupil bin, while in the younger group, this bin presents the lowest slope.

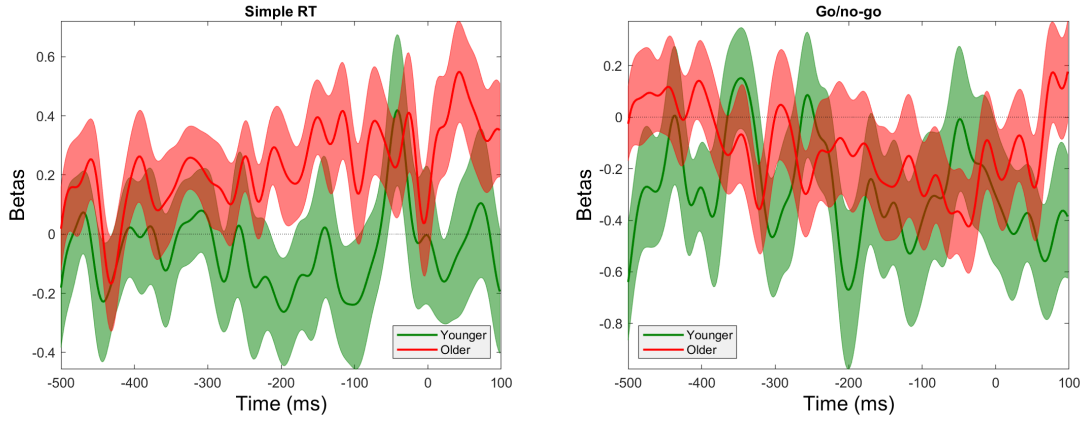


(a) **(b)**

Figure 5.16: Mean build-up rates of the response-locked CPP sorted by the preparatory pupil response, for both age groups in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

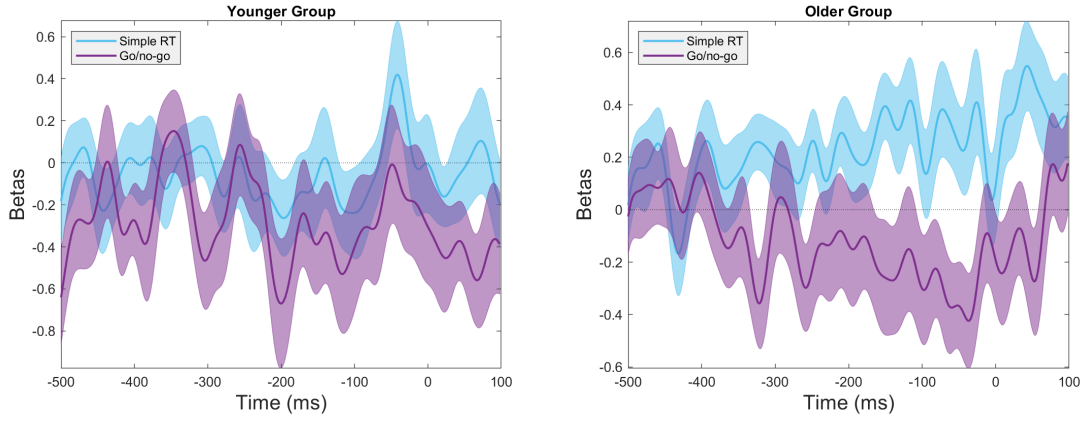
With regards to the significant Task × Group interaction, we previously saw that this arises from the fact that there is a difference between groups in the simple RT task (see Figure 5.3), in which the older group presents a steeper slope than the younger group, but no difference is found in the go/no-go task.

We also performed time point-by-time point correlation analyses between the CPP and the preparatory pupil response. After obtaining the beta parameters of each time point and each participant, we plotted their mean, which is represented in Figure 5.17 and 5.18. As expected by looking at these figures, the repeated measures ANOVA did not reveal any significant effects of group, task or group × task interaction.



(a) **(b)**

Figure 5.17: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the preparatory pupil response in a) the simple RT task, and b) the go/no-go task.



(a) **(b)**

Figure 5.18: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the preparatory pupil response in a) younger subjects, and b) older subjects.

However, there was a correlation between the CPP and the preparatory pupil, in the younger group during the simple RT task, from -164 ms to -120 ms, and from 20 ms to 74 ms (in the response-locked waveform), as revealed by the one sample t-tests.

5.3.2 Effect of the Pupil Baseline Diameter

Afterwards, we investigated the relationship between the baseline pupil diameter (tonic arousal levels) and the build-up rate of the CPP. First, we represented the time course of the CPP amplitude, binned in relation to the pupil baseline response, in Figure 5.19. Regarding the relation between tonic arousal and the build-up rate of the CPP, the results of the mixed ANOVA with two-within subject factors (task and tertile) and one between-subject factor (age group) showed that once again there is a significant Task × Group interaction [$F_{(1,70)} = 5.952$, $p = 0.017$], but no significant effects of tertile [$F_{(2,140)} = 2.540$, $p = 0.083$], task [$F_{(1,70)} = .002$, $p = 0.969$], tertile × group interaction [$F_{(2,140)} = .182$, $p = 0.834$], tertile × task interaction [$F_{(2,140)} = 1.761$, $p = 0.176$], three-way interaction task × tertiles × group [$F_{(2,140)} = 0.064$, $p = 0.938$], or a group effect [$F_{(1,70)} = .867$, $p = 0.355$].

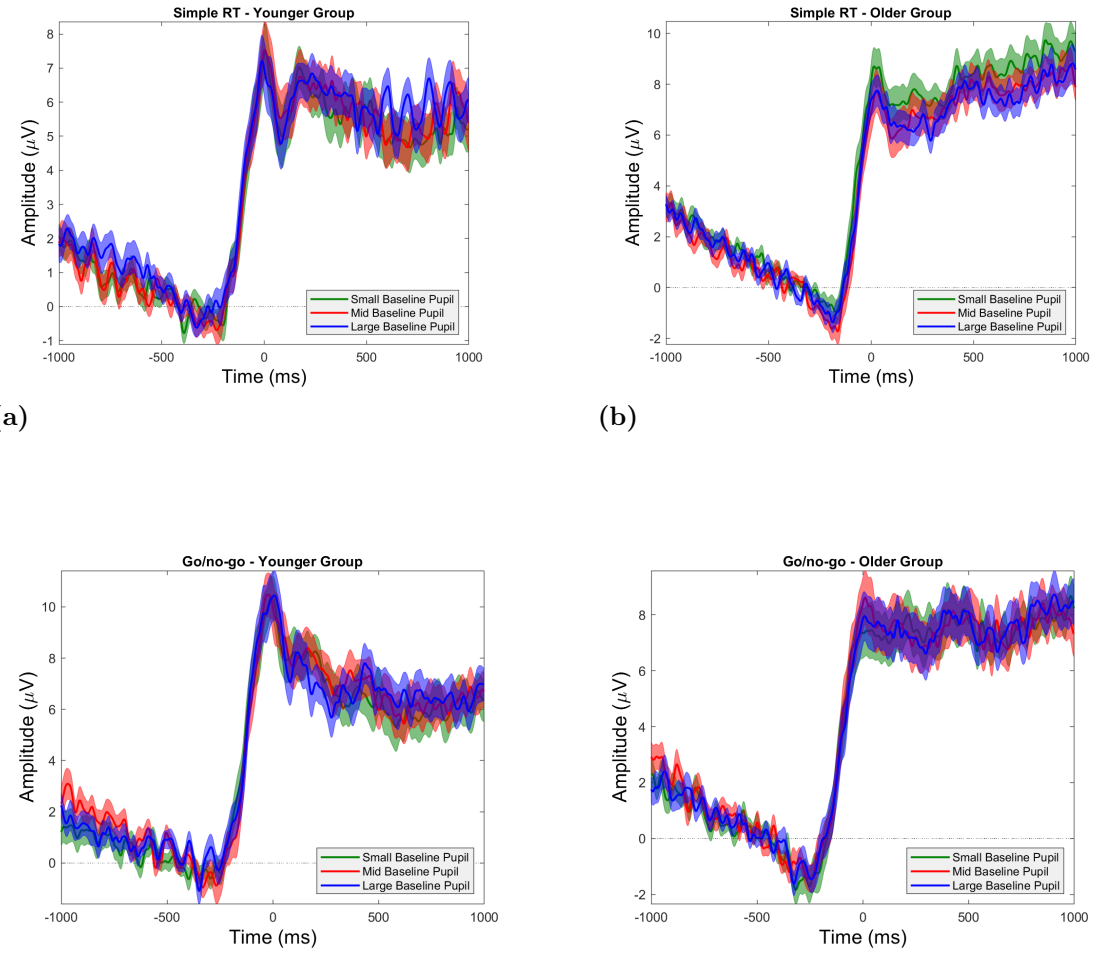
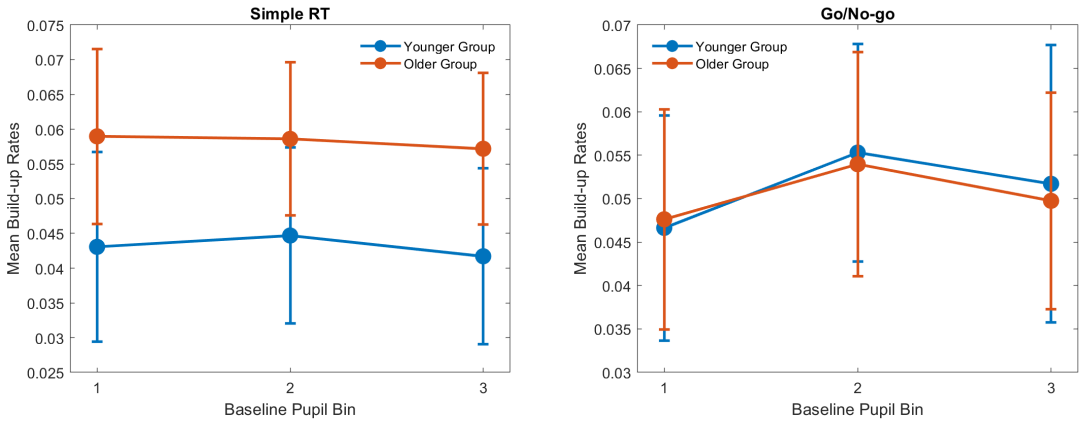


Figure 5.19: The response-locked CPP in relation to the baseline pupil diameter, in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.

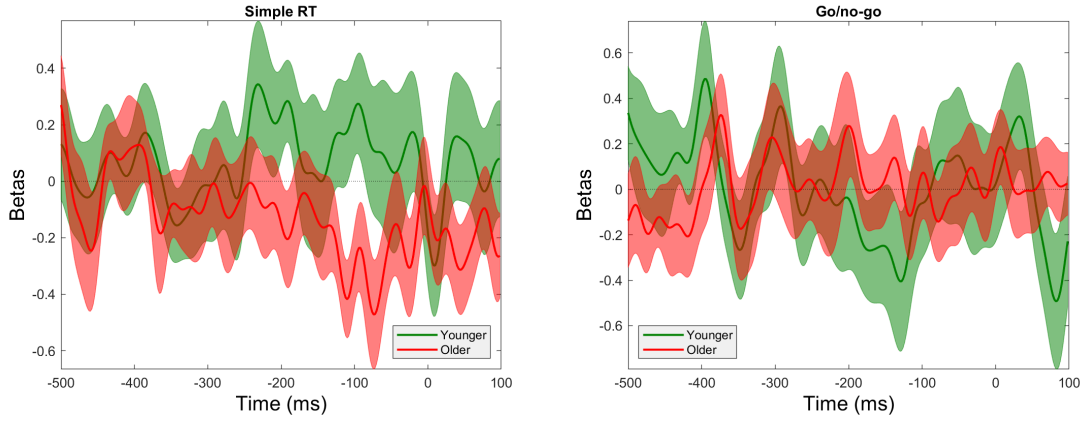
The following Figure 5.20 shows the mean build-up rates of the CPP of each baseline pupil bin, for each age group and task. Once again, these graphs show that the CPP build-up did not correlate with the baseline pupil diameter.



(a) **(b)**

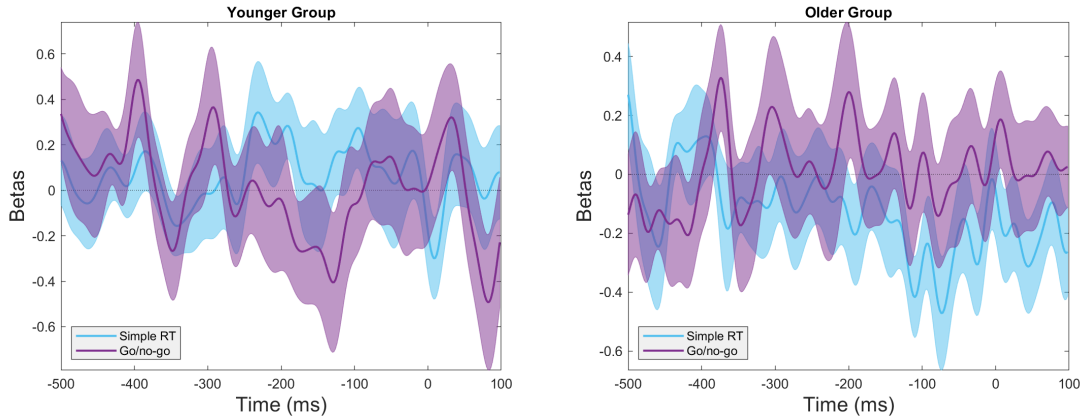
Figure 5.20: Mean build-up rates of the response-locked CPP sorted by the baseline pupil diameter, for both age groups in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

Finally, we performed time point-by-time point correlation analyses between the CPP and the baseline pupil diameter, using the LIMO toolbox. The mean of the beta parameters is represented in Figure 5.21 and 5.22. As expected by looking at these figures, and similarly to what happened when assessing phasic arousal, the repeated measures ANOVA didn't reveal any significant effects of group or task.



(a) **(b)**

Figure 5.21: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the baseline pupil diameter in a) the simple RT task, and b) the go/no-go task.



(a) **(b)**

Figure 5.22: Mean of the beta parameters obtained when performing correlation analyses between the response-locked CPP and the baseline pupil diameter in a) younger subjects, and b) older subjects.

The one-sample t-tests, which investigate if there are time windows where the betas are significantly different from zero, did not return any significant correlations, for any age group or task.

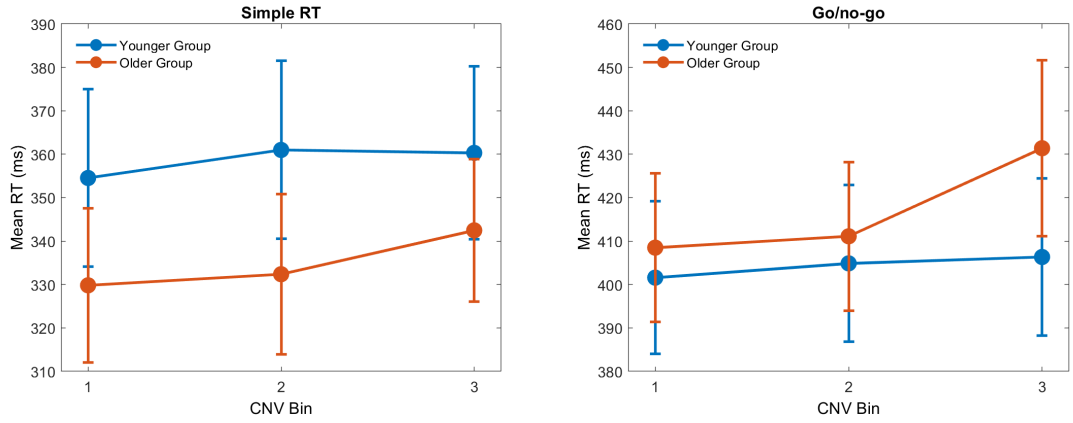
5.4 Relation between CNV and RT

We investigated if there is an effect of the CNV during the preparatory period before target onset in the RT. RT tasks are the preferred type of task for studying the CNV, which is a negative slow potential that occurs in the inter-stimulus interval, between a warning stimulus and an imperative stimulus (in the current study, between the cue and the target). In the past, the relationship between CNV and the RT has been reported as statistically significant. However, the majority of the evidence that supported this relationship was rather indirect, coming from studies in which authors manipulated a third variable, which either speeded up the response and amplified the CNV or slowed down the response and attenuated the CNV. Näätänen et al. (1974) [104] indicated several reasons as to why the evidence for such a relationship found in previous studies was not convincing, such as no registration of eye movements, RT data with very large variances, inclusion of only the fastest or the slowest reaction times, among others. In a review, Rebert and Tecce (1973) [105] came to the conclusion that CNV and RT are essentially unrelated events, despite frequently reported inverse correlations, and other authors supported that this relationship is highly dependent on the type of analysis attempted.

To investigate this relationship, we performed a mixed ANOVA with two within-

subject factors, the tertile and the task, and one between-subject factor, the age group. The results of this test revealed a significant effect of task [$F_{(1,70)} = 163.862$, $p < 0.001$], a significant Task × Group interaction [$F_{(1,70)} = 13.343$, $p < 0.001$], a significant effect of tertile [$F_{(2,140)} = 18.428$, $p < 0.001$], and a significant effect of interaction Tertile × Group [$F_{(2,140)} = 8.45$, $p < 0.001$]. There were not significant effects of the interaction Task × Tertile [$F_{(2,140)} = 1.242$, $p = 0.292$], meaning that the effect of tertile is similar in both tasks, no significant effect of the 3-way interaction task × tertiles × group [$F_{(2,140)} = 1.018$, $p = 0.364$], and no significant effect of group [$F_{(1,70)} = 0.232$, $p = 0.632$].

To further understand the dynamics of the Group × Tertile interaction, we plotted the mean RTs of each tertile, for both tasks and for both groups, which can be seen in Figure 5.23. By looking at these plots, we can see that the interaction Group × Tertile reflects the fact that in the older group, the effect of CNV in RT is greater than in the young group. This effect occurs in both tasks, which is evident in the non-significance of the 3-way interaction group × tertile × task (which means that the group × tertile interaction does not depend on the task).



(a) **(b)**

Figure 5.23: Mean RTs sorted by the CNV, for both age groups in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

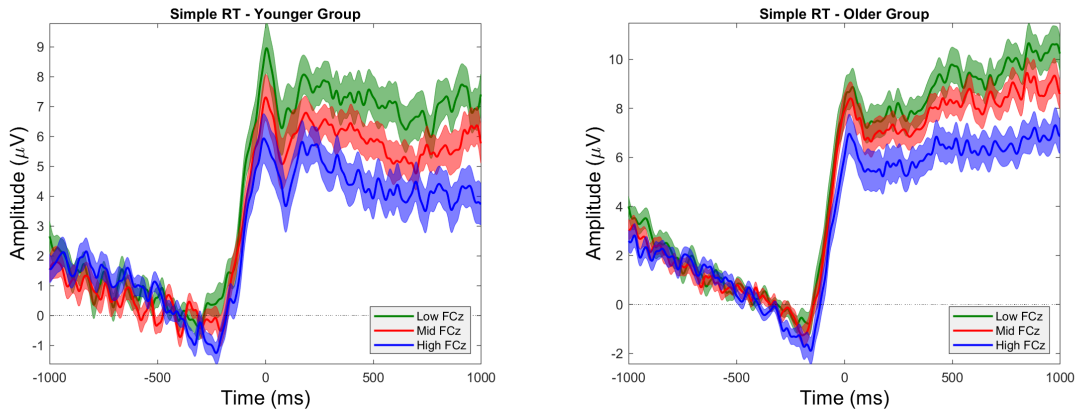
Overall, we conclude that the CNV affects the RT, such that more negative amplitudes of the CNV are associated with faster RTs. This leads us to hypothesize whether the CNV also affects the build-up rate of the CPP, which we will assess in the next section.

5.5 Relation between CNV and CPP

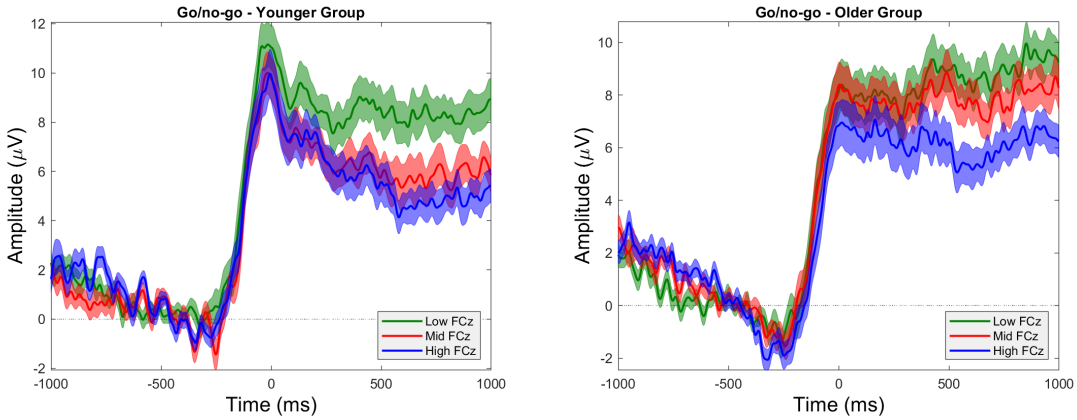
We investigated if there is an effect of the CNV during the preparatory period before target onset in the build-up rate of the CPP observed after target onset. The CNV reflects frontal cortical activation during the preparatory period before target onset and it is a measure of attentional control. The subfigures in Figure 5.24 show the CPP divided in tertiles according to the sorted CNV potential, for each task and each age group.

We performed a mixed ANOVA with two within-subject factors, the tertile and the task, and one between-subject factor, the age group. The results of this test revealed a significant Task × Group interaction [$F_{(1,70)} = 6.453$, p <0.015], and no significant effect of task [$F_{(1,70)}$ <.001, $p = 0.983$], tertile [$F_{(2,140)} = 2.454$, $p = .090$], tertile × group interaction [$F_{(2,140)} = 1.313$, $p = .272$], task × tertile interaction [$F_{(2,140)} = 1.078$, $p = .343$], three-way interaction task × tertiles × group [$F_{(2,140)} = .769$, $p = .465$], or group [$F_{(1,70)} = .754$, $p = .388$]. The significant Task × Group interaction indicates that the differences in the build-up rate between tasks depend on the group, which we had already seen.

To understand how exactly does the build-up rate of the CPP vary with the amplitude of the CNV before target onset, we plotted the mean build-up rates of each tertile, for both tasks and for both groups, which can be seen in Figure 5.25. These graphics show that in the simple RT task, the build-up rate tends to get steeper as the CNV gets more negative. This seems to be expected, because a steeper build-up rate is associated with a greater rate of evidence accumulation, and a more negative CNV is associated with a better preparation pre-stimulus. Therefore, it makes sense that a better preparation results in a greater rate of evidence accumulation. However, this effect of tertile was not quite statistically significant [$F_{(2,140)} = 2.454$, $p = .090$].

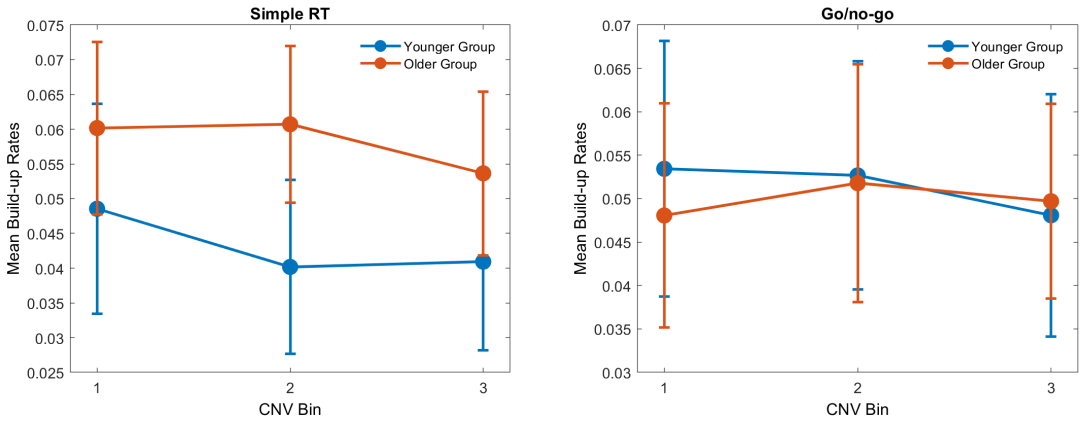


(a) **(b)**



(c) **(d)**

Figure 5.24: Response-locked CPP binned in relation to CNV, in a) younger subjects, simple RT task; b) older subjects, simple RT task; c) younger subjects, go/no-go task; d) older subjects, go/no-go task.



(a) **(b)**

Figure 5.25: Mean build-up rates of the response-locked CPP sorted by the CNV, for both age groups in a) the simple RT task, and b) the go/no-go task. Error bars represent 95% confidence intervals.

6

Conclusions

In the current project, we explored the impact of ageing on the rate of neural evidence accumulation, as well as whether there is a relationship between pupil-linked arousal, task performance, and the CPP build-up rate. We also investigated the relationship between task performance and pupil dynamics. Lastly, we assessed if the CNV, a measure of preparatory frontal activation, has an effect on the build-up rate of the CPP and on the RT.

From conducting this study, we were able to observe the following dynamics:

1. The target onset, i.e. an auditory tone of 1700 Hz, elicited an increasing positivity in the CPP until response latency.

2. We found no significant group differences in the build-up rate of the CPP. However, unlike the younger group, the older group did not modulate their build-up rate according to the difficulty of the task; their build-up rate was higher in the simple RT task, which requires only perception of the stimuli, than in the go/no-go task, which requires both perception and discrimination of the stimuli. At the same time, older adults took longer to respond in the go/no-go task than in the simple RT task, which suggests that the non-decision time components are higher in the older group. The fact that they present greater speed of accumulation of evidence, despite having slower non-decision time components, might indicate that they make a greater effort.

3. CPP correlated with RT, in both the simple RT condition and the go/no-go condition. Indeed, in faster trials the CPP build-up rate was steeper.

4. We found no correlation between the preparatory pupil response (a measure of phasic arousal) and the RT, for any age group or task. Similarly, we did not find any correlation between the baseline pupil diameter (a measure of tonic arousal) and the RT. Overall, we did not find tonic or phasic arousal to be predictive of behavioural performance.

5. CPP did not correlate with either the preparatory pupil response or the baseline pupil diameter. Differently to our results, van Kempen et al. (2019) [100] found that the CPP build-up rate correlated with pupil response, presenting steeper slopes in trials with largest pupil dilations. They also found that the baseline pupil diameter was not predictive of the CPP build-up rate.

6. We found a significant correlation between the CNV and the RT, such that more negative amplitudes of the CNV are associated with faster RTs.

7. The build-up rate of the CPP tended to get steeper as the CNV got more negative. This effect of tertile was not quite statistically significant, but it shows a trend in this direction.

Overall, we did not observe any relation between the arousal system and evidence accumulation, in younger or older adults, so this study does not allow us to conclude whether the arousal system is affected by ageing, and consequently we cannot point arousal as a biomarker of risk for the onset of neurodegenerative diseases. However, we found that ageing affected the modulation of the build-up rate with task difficulty. Older adults presented a faster build-up rate while engaged in the easier task condition, while young adults showed the opposite, a faster build-up rate in the more difficult task condition. This indicates that there are differences in the decision-making neural mechanisms between both groups.

6.1 Future Works

As mentioned in Chapter 3, there are several approaches to analyse EEG data. In this study, we chose to study ERPs, and specifically the CPP component, but it would have also been interesting to study event-related oscillations (ERO). In fact, ERO in the alpha, beta, gamma, delta, and theta frequency windows are highly modified throughout the cortex in pathologic brains, in particular from patients with cognitive impairment [94]. The first step to understand what could possibly cause the onset of brain-related diseases, is to study healthy individuals. Therefore, it would have also been possible to study the ERO, which are highly modified in pathological brains. Besides, ERO have already been studied in the context of evidence accumulation.

In the current study, we used data from a previous study in which Ribeiro et al. (2019) [44] recorded the EEG, the ECG and the pupillogram while participants performed a cued auditory task. We did not analyse the ECG data to investigate whether there is a relationship between the HRV and the evidence accumulation pro-

cess. The HRV is a physiological indicator that informs about the neural underlying of the decision-making process. Considering its association with decision-making, it is possible that it also changes with evidence accumulation. To the best of our knowledge, no studies thus far have investigated this association.

Previous studies have investigated other features of the CPP that were not assessable in our data, for instance the CPP onset. In the average waveform of our response-locked CPP data, and particularly at the latency of target onset, there is a negative peak which complicates the process of assessing these features. This negative peak is not found in other papers. Another limitation of this project is that the stimulus used in our task is not ideal for these studies, as it results in a very rapid accumulation of evidence. Stimuli like random dot kinematogram (RDK) would have been more adequate and previous studies using this type of stimuli were able to found significant differences between age groups.

Considering that one of the targets of our first project was response confidence and the main target of our second project is the evidence accumulation process, it is noteworthy to mention that there are studies regarding the importance of confidence on the evidence accumulation process. Specifically, Balsdon et al. (2020) [106] showed that observers' ability to set appropriate evidence accumulation bounds for perceptual decisions is strongly predictive of their ability to make accurate confidence judgements.

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