Neural Correlates of Working Memory in Chronic Primary Insomnia using The Sternberg Task: A Preliminary Analysis

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Abstract

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Kazem Habibi-Tanha

Chronic primary insomnia is characterized by difficulty falling sleep, maintaining sleep and waking up earlier than desired as well as daytime functioning impairment in the absence of an underlying neurological and psychological condition. Daytime functional impairment of patients with chronic primary insomnia is linked to cognitive deficits, including working memory. Functional neuroimaging studies investigating working memory in this population reported abnormal cerebral activation during cognitive abilities testing. This evidence could support altered cognitive functioning. Yet, the same results have not been replicated consistently. Hence, this study aims to provide a more nuanced evidence by identifying a map of cerebral activation among patients with insomnia in different phases of working memory using the Sternberg task. This task has never been used for this population. The Sternberg task can evaluate the working memory ability for the encoding and recall phases of working memory separately. Based on our results, we observed that many brain regions that were activated in patients with insomnia were similar to those that were activated in good sleepers in response to a working memory task. Yet, there were key regions within the frontal cortex that were not activated. The differences were more noticeable in the recall phase. This needs to be quantitatively verified by including a control cohort and investigated whether potential working memory impairment in insomnia is phase dependant in future studies. We extended the literature by identifying phase-dependant and load-dependent regions of cerebral activation and deactivation in patients with chronic primary insomnia during the Sternberg task.

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Contribution of Authors

Kazem Habibi-Tanha: Primary writer of the text, contributed to the design and implementation of the research, to recruitment of participants, to data collection and the analysis and interpretation of the results.

Dr. Florence Pomares: Project leader, contributed to the design and implementation of the research, to data collection, and assisted with the analysis and interpretation of the results. Provided input for the final version of the text.

Dr. Aurore Perrault: Project leader, contributed to the design and implementation of the research and to data collection.

Dr. Thien-Thanh Dang-Vu: Primary investigator, supervised and advised the project. Provided input for the final version of the text.

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List of Abbreviations

AASM: American Academy of Sleep Medicine

APA: American Psychiatric Association

ATP: Adenosine Triphosphate

BDI: Beck's Depression Inventory

BOLD: Blood-Oxygenation-Level-Dependent

DMN: Default Mode Network

DSM-V: The 5th Edition of Diagnostic and Statistical Manual of Mental Disorders

EEG: Electroencephalography

(f)MRI: (Functional) Magnetic Resonance Imaging

ICSD-3: The 3rd Edition of International Classification of Sleep Disorders

ISI: Insomnia Severity Index

KSS: Karolinska Sleepiness Scale

PET: Positron Emission Tomography

PSG: Polysomnography

SPM: Statistical Parametric Mapping

1. Introduction

1.1. Insomnia

1.1.1. What is Insomnia?

As the most common sleep disorder, chronic insomnia disorder is a significant public health problem that adversely affects six to ten percent of the adult population at one point or another in their life. In Canada, the prevalence of insomnia symptoms has increased by 42% among individuals aged 18 or older between 2007 and 2015 (Chaput et al., 2018). In addition, insomnia is likely to be gender-biased since nighttime insomnia symptoms are more common among females, and is linked with age since the frequency of their occurrence increases with age (Chaput et al., 2018; Ohayon, 2002). However, the findings are inconsistent concerning the prevalence of insomnia across different ethnicities (Morin & Jarrin, 2013).

The American Academy of Sleep Medicine (AASM) and the American Psychiatric Association (APA) have established a set of diagnostic criteria for chronic insomnia disorder in the third edition of the international classification of sleep disorders (ICSD-3) and the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-V) respectively. In both the ICSD-3 and the DSM-V, the diagnostic criteria for insomnia are listed as sleep latency more than 30 minutes, wake after sleep onset greater than 30 minutes and/or early awaking by at least 30 minutes. Sleep latency is defined as the time interval between going to bed and initiation of sleep. Wake after sleep onset is defined as the total duration of wakefulness between initiation of sleep and last awaking. These symptoms, which are subjective, must be present in addition to subjective daytime functioning impairment for the diagnosis of insomnia (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013). According to both the ICSD-3 and the DSM-V, the diagnosis of chronic insomnia requires that aforementioned symptoms occur at least three times a week for more than three months (American Psychiatric Association, 2013).

Although a set of diagnostic criteria for chronic insomnia exists, there is a lack of a consistent definition and standardized assessment procedure in the literature due to heterogeneous nature of the insomnia disorder (Morin & Jarrin, 2013). The DSM-V classifies insomnia disorder into primary insomnia and secondary insomnia (American Psychiatric Association, 2013). While primary insomnia is presented as a stand-alone condition, secondary insomnia is co-morbid with other sleep-related,

neurological or psychiatric disorders (American Psychiatric Association, 2013). Prior to this dichotomized classification, the AASM specified eleven subtypes of insomnia disorder in the second edition of ICSD (Thorpy, 2012). But, in its most recent edition, the AASM elucidates that we currently cannot reliably distinguish between different types and subtypes of insomnia. Therefore, they suggest referring to all types of insomnia as chronic insomnia disorder (American Academy of Sleep Medicine, 2014). The lack of consensus regarding the number of types of insomnia further provides us with evidence that insomnia has diverse characteristics and could be presented differently between individuals. Heterogeneous nature of insomnia may also explain the absence of a universally accepted model for the pathophysiology and the etiology of this disorder.

For the purpose of this research project, we recruited individuals with chronic primary insomnia. Hereinafter, the term "chronic primary insomnia" and "insomnia" will be used interchangeably. The instances where the word "insomnia" does not refer to "chronic primary insomnia" are specified.

1.1.2. Pathophysiology and nature of Insomnia

The etiology and nature of insomnia disorder have been studied on genetic, cellular, neuroanatomical, physiological and psychological levels. While progress has been made and some promising hypotheses have been generated, there is still an ongoing debate about the pathophysiology of the insomnia disorder (Bonnet & Arand, 2010; Levenson et al., 2015).

One of the most comprehensive hypotheses is the hyperarousal theory of insomnia (Bonnet & Arand, 2010). This theory includes a cognitive-behavioural component and a physiological component. The cognitive-behavioural component explains that a number of factors, which are divided into three categories of predisposing, precipitating and perpetuating insomnia, may contribute to the development and maintenance of the insomnia disorder (Dikeos & Soldatos, 2005; Spielman et al., 1987). Predisposing factors are biological and demographical elements, such as age, sex and heritable behaviours that make an individual more susceptible to insomnia. Precipitating factors are the events and major stressors that trigger the onset of acute insomnia. Perpetuating factors are compensatory behaviours that can associate sleep stimuli with wakefulness that leads to worsening and maintenance of insomnia. For instance, an individual who experiences acute insomnia, due to a traumatic life event, stays in bed for a longer duration in hope of falling asleep or actively tries to fall asleep. Repetition of this behaviour over time conditions this person to associate the sleep-promoting stimuli, such as their own bed and a dark room, with wakefulness.

The physiological component of the hyperarousal theory indicates that individuals with insomnia experience an unusual amount of physiological arousal (Bonnet & Arand, 2010). In the early days of sleep research, Monroe showed that poor sleepers have increased body temperature, vasoconstriction, body movement and skin resistance compared to healthy good sleepers before and during sleep (Monroe, 1967). Vasoconstriction seen in this seminal study was later attributed to increased activity of sympathetic nervous system and hypothalamus-pituitary-adrenal axis, particularly in patients with insomnia who are considered short-sleepers (Barnett & Cooper, 2008; Bonnet & Arand, 2010; Irwin et al., 1999). Over the past three decades, many other studies have refined the previous experiments and have investigated other physiological measures among patients with primary insomnia. Some of these studies showed that patients with primary insomnia experience a higher heart rate, lower heart rate variability, abnormal hormonal secretions and elevated body temperature during sleep and wake (Backhaus et al., 2006; Lushington et al., 2000; Rodenbeck & Hajak, 2001; Stepanski et al., 1994). Heart rate and heart rate variability can be used as indices of autonomic control during sleep. Heart rate variability is the change in duration between two consecutive heartbeats. A lower heart rate variability is usually suggestive of a better sleep quality. This measure is under the regulation of various physiological systems, including the autonomic nervous system. Another physiological alteration in patients with insomnia is increase in high-frequency brain waves (i.e. Beta wave: 14 – 30 Hz; Gamma wave; > 30Hz; Niedermeyer, 1999) and decrease in low-frequency brain waves, such as delta (0.1-3.5 Hz) brain's electrical activity or electroencephalogram activity during the non-rapid eye movement part of sleep. Normally, the brain waves during non-rapid eye movement sleep tend to have a higher amplitude and a lower frequency. Increase in high-frequency brain waves may be attributed to a more pronounced presence of sympathetic activity during sleep in patients with insomnia. A few other Studies showed similar results. The patients in these studies had higher gamma and beta waves during sleep compared to healthy good sleepers and the activity of delta waves was diminished in this population (Krystal et al., 2002; Merica et al., 1998; Perlis et al., 2001). An increase in the high-to-low EEG frequency ratio is associated with poorer quality of sleep and can blur the line between sleep and wakefulness (Krystal & Edinger, 2008; Maes et al., 2014). Also, the high-frequency brain electrical activity is associated with higher cerebral metabolism (Ingvar et al., 1979). So, their increase can be a sign of heightened cortical and central nervous system activity during sleep. The nuance of the relationship between neuronal activity and brain metabolism has not been identified. It is thought that most of the energy required for the functioning of the brain is used by the activated neurons at the synaptic cleft. The bulk of this energy is needed to restore the neuronal membrane potential following depolarization. The activity at the synaptic cleft of the activated neurons lead to a change in cerebral blood flow, an indirect measure of cerebral metabolism, of the activated brain region (Sheth et al.,

2004). The change in cerebral blood flow can be explained by various mechanisms, one of which is the astrocyte-neuron lactate shuttle hypothesis. According to the astrocyte-neuron lactate shuttle hypothesis, astrocytes contribute to anaerobic conversion of glucose to lactose (Brown et al., 2004; Pellerin et al., 2007). The produced lactose then undergoes oxidative metabolism by neurons leading to an increase demand for oxygen thereby augmenting regional cerebral blood flow as needed. Moreover, Positron Emission Tomography (PET) showed that increase of fast-frequency brain waves and decrease of the slow-frequency brain waves, a sign of increase in sympathetic activation, are associated with elevated activation of the thalamus, brainstem reticular formation, anterior cingulate cortex and orbitofrontal cortex (Hofle et al., 1997; Nofzinger et al., 2000). Normally, reticular formation neurons, responsible for arousal promotion, decrease their firing to inhibit the relay of sensory information from the thalamus to cortical regions in an attempt to promote sleep (Jones, 2011). As a result, lack of decrease in activity of reticular formation and the thalamus during sleep can leave individuals vulnerable to sleep disruption. Due to conflicting evidence, patients with insomnia do not necessarily have a higher gamma or beta wave activity during wakefulness (Wolynczyk-Gmaj & Szelenberger, 2011; Y. M. Wu et al., 2013).

Neuroimaging findings also provide evidence supporting the hyperarousal theory and give insight into how glucose metabolism is possibly altered in patients with chronic primary insomnia (Kay et al., 2016; Reviewed in O'Byrne et al., 2014). PET studies, measuring glucose metabolism, have shown that the global brain metabolism of patients with insomnia is higher than good sleepers across wake and different states of sleep. Individuals with insomnia also experience a lower global brain metabolism reduction from wakefulness to sleep compared to good sleepers (Kay et al., 2016; Nofzinger et al., 2004). This may be another indication of heightened physiological arousal among patients with insomnia and a sign of dysregulation of arousal and sleep prompting networks. Yet, PET studies also identified several regions that are hypoactivated during wakefulness in patients with insomnia in comparison with good sleepers. Specifically, these regions are involved in higher cognitive functioning, including working memory and integration of cognitive and affective information, such as the prefrontal cortex, posterior cingulate cortex and thalamus, show lower metabolism in patients with insomnia compared to good sleepers during wakefulness (Frith & Dolan, 1996; Kay et al., 2016; Nofzinger et al., 2004; Smith et al., 1998). The findings of Kay et al. and Nofzinger et al. are also partially corroborated by a fMRI study by Altena and colleagues. (Altena, Van Der Werf, Sanz-Arigita, et al., 2008). More specifically, this fMRI study, which used a letter fluency task, demonstrated that left medial prefrontal cortex and left inferior frontal gyrus are hypoactivated in response to this task among patients with chronic insomnia compared to healthy participants. In other studies, different regions impacted by hypometabolism in patients with insomnia are occipital and parietal cortices. To

clarify, these studies reported hypoactivation in these specific regions in response to a cognitive task and stimuli. This is different from earlier presented studies where they provided evidence for a higher global metabolism of brain in patients with insomnia as these studies obtained their results in a rested state without any stimuli. Many of the hypoactivated regions in response to cognitive stimuli are part of the frontoparietal network that contributes to sustained attention and working memory (Brühl et al., 2014; Kay et al., 2016; Longe et al., 2010; Nofzinger et al., 2004). Altered activity of regions within this primary network in response to cognitive tasks compared to healthy good sleepers maybe an indication of changed cognitive functioning in patients with insomnia. It is important to note that intact attention is the prerequisite for normal cognitive functioning. Hence, a potential alteration of normal attention ability can lead to cognitive impairment in other domains. Lower metabolism in cortical and sub-cortical brain regions have also been shown in the first PET study investigating the effects of total sleep deprivation on regional cerebral glucose metabolism during wakefulness (J. C. Wu et al., 1991). Therefore, altered regional cerebral glucose metabolism in patients with insomnia may be a physiological adaptation in response to chronic partial sleep deprivation. Besides, alterations in cerebral metabolism in previously mentioned regions may contribute to the negative impact of insomnia on objective and subjective cognitive functioning that are explained further on in this paper.

Nevertheless, we need to be cautious when we describe the hyperarousal theory as an etiological factor for insomnia. While there is compelling evidence that suggests the hyperarousal theory could explain the etiology of insomnia, there are other points that need to be considered. For instance, we are not exactly sure whether insomnia is caused by the markers of hyperarousal, or these markers are simply by-products of insomnia. In addition, there are also studies that fail to provide evidence in support of physiological hyperarousal in patients with primary insomnia (Reviewed in Kay & Buysse, 2017). For instance, a study, in which participants were under a 24-hour constant supervision in a controlled environment, found that physiological indices, such as temperature, cardiac activity and hormonal activity were not significantly different between the participants with chronic insomnia and healthy good sleepers (Varkevisser et al., 2005). As a side note, this experiment was done in a controlled environment, under strict protocol routine, to eliminate masking effects. In other words, certain behaviours, such as irregular time of food intake and amount of physical activity were limited, that could have an impact on the outcome were eliminated. Thus, a more complex model than the hyperarousal theory may be needed to fully explain the pathophysiology of insomnia.

1.1.3. Cognitive impacts of Insomnia

The impact of insomnia goes beyond difficulty falling asleep or unsatisfactory sleep quality during the night and extends into how individuals perform or feel during the wakefulness (Morin &

Benca, 2012). Individuals with insomnia usually experience fatigue and are more irritable throughout the day. Insomnia is also associated with decreased quality of life, decreased productivity and increased absenteeism at work (Daley et al., 2009; Morin & Jarrin, 2013). In addition, patients with chronic insomnia are more prone to psychiatric disorders, such as depression, anxiety and substance misuse (Morin & Jarrin, 2013; Roth et al., 2006). The cognitive functioning of this population has also been reported to be impaired. The next paragraph further elaborates on this point.

With regard to cognition, insomnia is associated with cognitive deficits contributing to the daytime functioning impairment, one of the diagnostic criteria of insomnia (American Psychiatric Association, 2013). Cognitive performance of patients with both chronic primary insomnia or secondary insomnia have been assessed subjectively (i.e. self-report measures) and objectively (i.e. cognitive tasks or psychomotor tests) by cognitive domains. For instance, Joo et al. assessed multiple cognitive domains of twenty-seven patients with chronic primary insomnia (25 females; age: 51.2 ± 9.6 y.o.) and observed that patients with insomnia had a worse working memory, visual memory, verbal memory and verbal fluency compared to a control group (28 females; age: 50.4 ± 7.1 y.o). However, the flexibility aspect of executive function of patients with insomnia was comparable to the performance of the control group (Joo et al., 2014). Additionally, Fortier-Brochu and colleagues found that a group consisting of insomnia patients with and without subjective cognitive impairment (25 participants, 14 females, age: 44.4 ± 11.5 y.o.) had a significantly worse performance in regards to attention as well as episodic memory compared to a group of healthy good sleepers (16 participants, 8 females, age: 42.8 ± 12.9 y.o.). Similarly, they had a comparable executive function performance (E. Fortier-Brochu & Morin, 2014). These studies did not specify at what point during the circadian rhythm the participants were required to perform the cognitive ability assessments. However, there is evidence that attention capacity which is essential for cognitive performance can fluctuate during the day and it reaches the lowest levels late at night and early morning (Valdez, 2019). Hence, it is important to conduct cognitive capacity testing at a consistent time during the day for all participants. The researchers also noted that patients who associated their insomnia symptoms with daytime functioning impairment had a poorer performance on cognitive tasks (e.g. various difficulty levels, reaction time and percent accuracy). In contrast, a study investigating a handful of cognitive capacities among patients with chronic primary insomnia found that they performed similarly on these domains, which included executive function and memory (Sivertsen et al., 2013). However, the subjective memory performance of patients with insomnia was significantly worse than that of the good sleepers.

Ultimately, while some individuals with insomnia complain about cognitive impairments, certain studies were unable to demonstrate that individuals experience cognitive impairment using

objective assessments. Nonetheless, meta-analyses demonstrated that insomnia negatively impacts certain cognitive domains, such as working memory, episodic memory and problem solving of executive function objectively (Wardle-Pinkston et al., 2019; É. Fortier-Brochu et al., 2012). However, studies included for these meta-analyses used participants with a wide range of insomnia severity and type, hence subjective assessment was not performed separately for every cognitive domain. Therefore, the results cannot necessarily explain the discrepancy between objective and subjective performance among patients with chronic primary insomnia.

1.1.4. Discrepancy Between Objective and Subjective Performance

The discrepancy between objective and subjective cognitive performance of patients with insomnia can be attributed to multiple potential reasons. First, insomnia impacts certain cognitive domains that are essential in carrying on complex and routine tasks throughout the day, such as working memory, episodic memory and the problem-solving aspect of executive functions. Since these domains of cognition are needed more often due to their importance, even mild deficits in these domains could lead to daytime functioning impairment and an exaggerated perception of cognitive deficit (É. Fortier-Brochu et al., 2012; Marcotte et al., 2010). Second, many of the cognitive tests used in insomnia studies have been designed and validated to examine major deficits in individuals with brain injury or neurological disorders. The cognitive impairments among patients with insomnia may be mild. Consequently, these tests may not be sensitive enough to detect mild cognitive deficits in patients with insomnia (É. Fortier-Brochu et al., 2012). Third, chronic sleep restriction studies demonstrated that cognitive impairment, due to a lack of adequate sleep, increases with additional nights of sleep deprivation. However, cognitive performance recovers after one night of good sleep (Banks et al., 2010; Van Dongen et al., 2003). The quality of sleep in patients with insomnia is not consistent across different nights. These patients can have satisfactory sleep on some nights of the week, but, as long as they have unsatisfactory sleep (i.e. sleep onset latency longer than 30 minutes, wake period after sleep onset for a period of longer than 30 minutes and wake up earlier than desired by 30 minutes) on at least three nights of a week, they are considered to have insomnia-like symptoms (Vallières et al., 2005). Hence, this night-to-night variability may lead to differences in cognitive performance of individuals with insomnia. Lastly, previous fMRI findings show that regional brain activity (an indirect measure of brain metabolism) of individuals with chronic primary insomnia are altered (Reviewed in Cross & Dang-Vu, 2019; O'Byrne et al., 2014). Kay and colleagues found that the metabolism of brain regions are involved in self-criticism are altered in patients with chronic primary insomnia (Brühl et al., 2014; Kay et al., 2016; Longe et al., 2010). Namely, the lateral prefrontal cortex and lingual gyrus in the

occipital region of the brain. Therefore, it is possible for this population to misperceive their cognitive performance and have an inaccurate sense of their cognitive impairment.

1.2. Working Memory

1.2.1. Organization of Working Memory

Working memory is defined as the capacity to retain and manipulate information for short periods of time. It can be broken down into three phases: encoding the new information, retaining the information and manipulating the information (Baddeley, 1992). In addition, different components of working memory rely on other cognitive domains. The encoding aspect of working memory is attention-driven, the retrieval or manipulation aspect of working memory depends on episodic memory. Executive function controls the flow of information (Baddeley, 2000). As a result, impairment of other cognitive domains may have a negative impact on working memory. Working memory is particularly important because it is involved in learning and using language, planning, mental arithmetic, stringing ideas and thoughts, decision-making and task execution (Baddeley, 1992; Baddeley, 2003; DeStefano & LeFevre, 2004; Marcotte et al., 2010). Hence, working memory is essential in carrying out a wide range of tasks; whether it is a simple task like repeating a word, or a more sophisticated task like planning and executing a chess move. Consequently, even the slightest working memory deficit may exhibit a subjective daytime functioning impairment.

Depending on the cognitive task we intend to perform, we encode and store different types of sensory information (input), such as verbal material or visual input (Baddeley, 1992, 2000). Likewise, our intention determines how we manipulate the retained information and what type of output we produce (e.g. carrying on a conversation, driving in a straight line, executing a chess move, etc.). The flow of sensory input between the three phases of working memory has been described by its multiple-component model (Alan Baddeley, 1992, 2000, 2003). Essentially, this model explains that human working memory has four fundamental elements: the central executive, phonological loop, visuospatial sketchpad and episodic buffer. According to this model, the central executive part prioritizes the incoming information by assigning the verbal information to the phonological loop where this information is stored and assigning the visual and spatial input to the visuospatial sketchpad, where this information is integrated and retained. The last component of working memory, episodic buffer, has the capability to retrieve information from multiple sources, such as long-term memory. It can then be integrated with the retained information for the purpose of manipulation with the help of the executive function, and temporarily store this information. The retained information in the phonological loop, visuospatial sketchpad or episodic buffer can then be retrieved by the central executive function to produce an output (A. Baddeley, 1992; Alan Baddeley, 2000).

There are multiple paradigms that researchers have been using to assess working memory capacity of participants in research studies (Rottschy et al., 2012). Our working memory of interest is the Sternberg task. The Sternberg task is divided into multiple trials where each trial consists of two parts. The first part presents several stimuli one after the other. During the second part, a target is shown, and participants need to decide whether the target was amongst the series of stimuli (Figure 5). There have been successful studies that used different variations of the Sternberg task in healthy individuals to demonstrate a breakdown in participant's cognitive performance in response to an increase in cognitive load. The variation between versions of the Sternberg have not impeded its ability to show a breakdown in the performance of participants with an increase in difficulty (Altamura et al., 2007; Ashida et al., 2019; Duncko et al., 2009; Sternberg, 1966). An example is a study done by Ashida et al. (n= 19) that used a verbal version of the Sternberg task with four difficulty levels and a steeper increase in cognitive load compared to our working memory paradigm (Ashida et al., 2019). The stimuli used in the task of this study were letters and the task had four levels of difficulty. In addition, the durations of delay between the encoding phase and the recall phase rotated between three, four and five seconds. Their results showed that the performance of the participants deteriorated, in terms of reaction time (i.e. increased). Post-hoc analysis showed that this effect was driven by the highest difficulty level. Another study (n=18) using letters as stimuli, for the Sternberg task, with three levels of difficulty and two variations of maintenance duration found similar results (Altamura et al., 2007). The same results were replicated by Duncko et al. (n=11) that used a version of the Sternberg task with three difficulty levels (Duncko et al., 2009). Similar to previous studies, they used letters as their stimuli, but the duration of encoding period was shorter (750 ms). Each level of difficulty contained two, three and four letters respectively. The findings of these studies are also in line with the results of the first study that employed this paradigm to assess memory (Sternberg, 1966). While there are differences between the versions of the Sternberg task used in different studies, the evidence suggests that an increase in cognitive load can challenge the working memory capability of the participants.

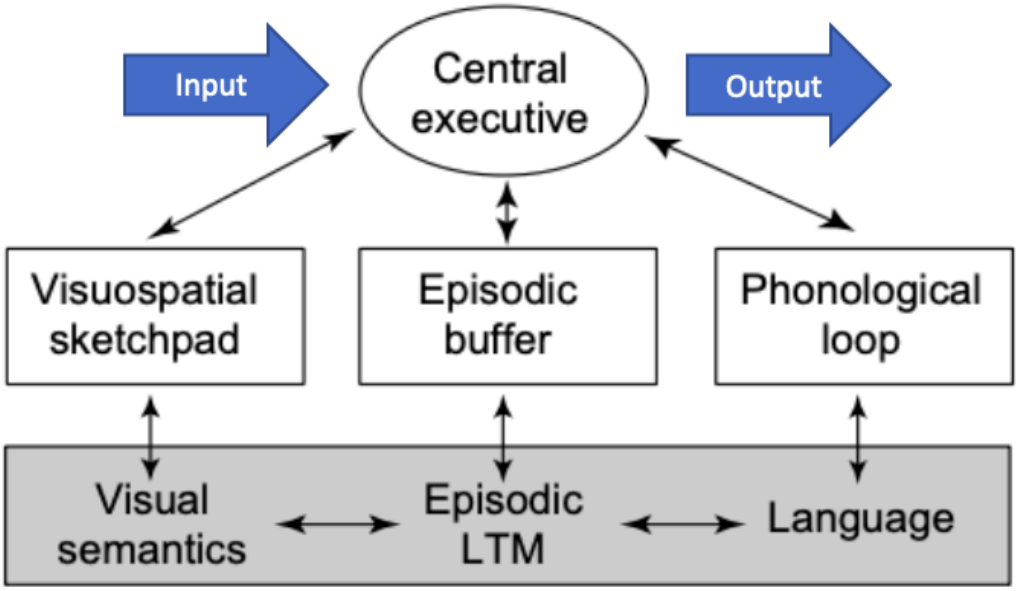


Figure 1: Schematic representation of the multi-component model of working memory. Shaded area represents the aspect of memory that can store information for long-term and accumulate knowledge, also known as the "crystallized" aspect of memory. The unshaded areas represent the four components of the working memory, also known as the "fluid" aspect of cognition (A. Baddeley, 1992; Alan Baddeley, 2000).

1.2.2. Neural Correlates of Working Memory

Modality of sensory information (e.g. verbal vs. non-verbal) that can be encoded and retained in our working memory can vary based on our intention, and lead to different operations (e.g. repeating a word, finger tapping, etc.). Literature shows that different types of input to encode or manipulate as well as different forms of recall in a working memory task may render different patterns of brain activation (Archer et al., 2018; Drummond et al., 2013; Paskavitz et al., 2010; Rottschy et al., 2012; Son et al., 2018). The three categories of working memory tasks that have commonly been used in the literature are the N-back task, Sternberg task and delayed matching to sample (Rottschy et al., 2012). During the N-back task, a series of consecutive stimuli are presented to participants. They need to decide whether the current stimulus is the same as the stimulus "n" turns back, where the value for "n" is variable. The Sternberg task was explained in the previous paragraph. During the delayed sample match, a single stimulus is presented. Subsequently, participants need to detect the stimulus among a set of multiple stimuli. The type of stimuli in these tasks can vary between letters, words or digits to shapes, sounds or verbal cues. Likewise, the recall aspect of the task can either be pure retrieval or involve manipulation and mental arithmetic.

A meta-analysis investigated the findings of 189 functional neuroimaging studies that used a working memory task to define a core network for working memory. This paper described the network as "core working memory network" (Rottschy et al., 2012). The results of this meta-analysis demonstrate that different stimuli (input), contrasts and recall type can render different patterns of brain activation. Yet, there are regions that are always associated with working memory regardless of the task design, contrast or recall mode used in the studies. These regions are located bilaterally in the frontal and parietal regions of the brain. More specifically, the core working memory network includes the medial frontal cortex, inferior frontal gyrus, intraparietal cortex and anterior insula. Rotteschy et al. define these regions as the working memory core network (Figure 2). Nonetheless, it is important to be aware of different working memory designs as they generate different patterns and can be a source of inconsistency between studies. For instance, this coordinate-based meta-analysis shows that working memory tasks with a verbal component consistently activate the left Broca's region, in addition to other working memory-related cerebral regions. This plays an important role in the production of speech and non-verbal working memory task by consistently activating the dorsal and medial premotor areas (Broca, 1861; Lazar & Mohr, 2011; Rottschy et al., 2012). Again, this evidence highlights the importance of working memory task design and makes it evident that different working memory tasks can generate different brain activation patterns. Consistent with the idea that two different working memory designs yield dissimilar brain activation pattern, the two widely used working memory tasks,

the N-back and Sternberg tasks, also activate different cerebral regions (Rottschy et al., 2012). It is not within the scope of this paper to compare these two working memory paradigms in detail. However, the next paragraph summarizes findings of some of the fMRI studies that employed the Sternberg task in healthy participants. This is a summary of what can be expected to be observed in a healthy brain as our data cannot provide any insights on this. Hence, these studies can be a reference point for us to qualitatively compare our results with.

A study by Ashida et al. (n= 19, 14 females, median age: 27.5 y.o., range: 23-44 y.o.) used a verbal version of the Sternberg task with four difficulty levels among healthy participants (Ashida et al., 2019). The lowest difficulty level contained two stimuli and the subsequent difficulty levels contained four and six stimuli respectively with the highest difficulty level containing eight letters. In addition, the durations of delay between the encoding phase and the recall phase rotated between three, four and five seconds. The performance of participants was poorer in higher levels. The results of this study demonstrated that frontal pole, insular cortex, frontal operculum, precentral gyrus, paracentral gyrus and occipital cortex were activated during the encoding phase. The maintenance phase of the Sternberg task elicited brain activity in the middle frontal gyri bilaterally, paracingulate gyrus, insular cortex, and frontal operculum. As for the recall phase, Ashida and colleagues observed cerebral activation in left precentral and post central gyri and bilateral inferior frontal gyrus and occipital cortex. Laterality for some regions were not specified. Another fMRI investigation (n= 18, 7 females, median age: 27.5; SD was not disclosed) using the Sternberg task in healthy participants used letters as the stimuli for the task (Altamura et al., 2007). Their task included three levels of difficulty and two variations of maintenance duration. The findings of this study showed that activated clusters during the Sternberg task, across difficulty levels and phases, are located in bilateral dorsolateral prefrontal cortex, left Broca's area, right ventrolateral prefrontal cortex, right insula, bilateral supplementary motor cortex, bilateral premotor area, bilateral posterior parietal lobe, right precuneus, left inferior temporal lobe, bilateral ventral posterior cingulate cortex. Additionally, Altamura and colleagues observed that an increase in set size of trial was associated with higher activation in bilateral dorsolateral prefrontal cortex, supplementary motor areas, premotor areas, bilateral posterior parietal areas, Broca's area, and right ventrolateral prefrontal cortex. This observation was independent of the maintenance phase duration. Moreover, they demonstrated that activation in left supplementary motor area, left premotor area and left Broca's area increased in response to a longer maintenance phase duration. Lastly, Altamura and colleagues observed that regions within the prefrontal cortex are exclusively recruited in response to an increase in set size. As such, an increase in delay duration does not elicit activation of these regions nor are they activated during the maintenance phase. Another study that attempted to describe the cerebral regions that are activated in response to each phase of working memory during

the Sternberg task was conducted by Cairo and colleagues (Cairo et al., 2004). This study (n= 18, 10 females, mean age: 27.5, range: 18-35 y.o., SD was not disclosed) employed consonants as stimulus of the task. Their working memory paradigm's conditions depended on the combination of set size and the duration of the delay (e.g. 3 seconds delay/4 letters). The working paradigm used in this study contained four different cognitive loads that differed between 2, 4, 6 or 8 uppercase letters. Participants were required to remember the stimuli presented to them for a short period of time. The maintenance phase varied between 3, 4 and 5 seconds. Neuroimaging findings for this investigation were reported based on average brain activation across all cognitive load conditions similar to previously presented studies. Results of this experiment indicated that supplementary motor area/cingulate motor area, bilateral precentral gyrus, bilateral inferior frontal gyrus, right middle frontal gyrus, bilateral inferior parietal lobule, bilateral precuneus, right superior parietal lobule, bilateral temporal lobe, bilateral occipital lobe were activated in response to the encoding phase of the task. As for the maintenance phase, they observed that it elicited brain activation in supplementary motor area, left precentral gyrus, bilateral superior frontal gyrus, left inferior/middle frontal gyrus, right middle frontal gyrus, left parietal-precuneus and bilateral occipital lobe. Finally, regions that were activated in during the recall phase of the working memory paradigm included supplementary motor area, left precentral gyrus, right inferior frontal gyrus, right middle frontal gyrus, bilateral insula, bilateral superior parietal lobule, bilateral postcentral gyrus, right occipital lobe, left middle temporal gyrus and right inferior temporal gyrus.

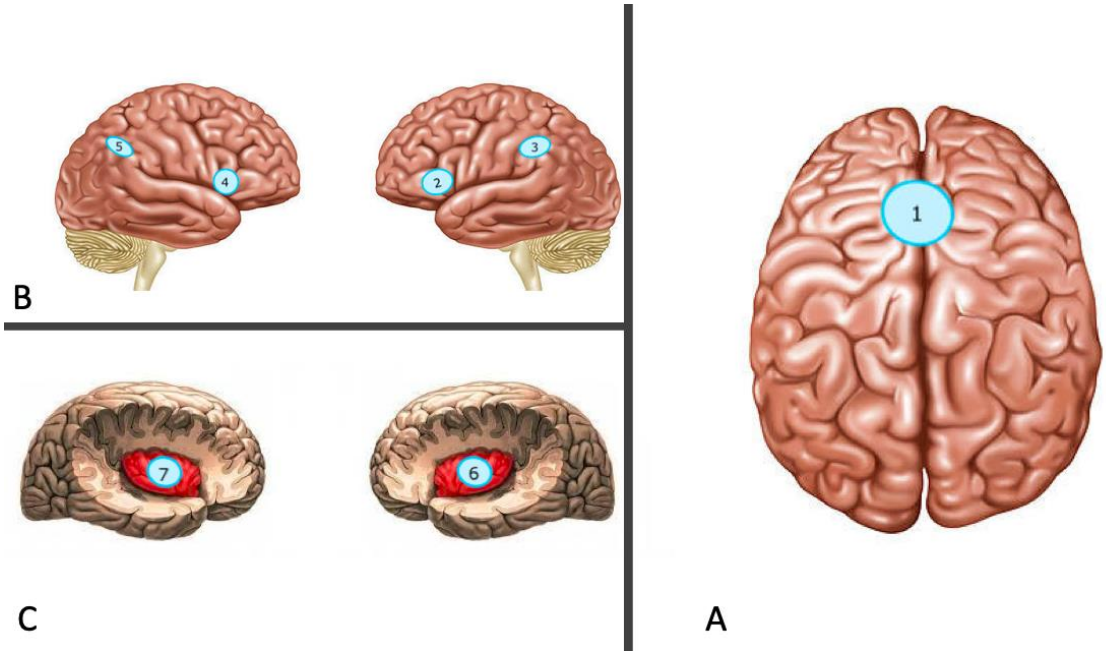


Figure 2: Common brain regions that are activated during a working memory task. **A) Superior view 1.** Left and right medial frontal cortex **B) Lateral view 2.** Left inferior frontal gyrus pars opercularis/ caudal lateral prefrontal gyrus **3.** Left intraparietal cortex **4.** Right inferior frontal gyrus pars opercularis/ caudal lateral prefrontal gyrus **5.** Right intraparietal cortex **C) Lateral view of the insula lobe 6.** Left anterior insula **7.** Right anterior insula (Rottschy et al., 2012).

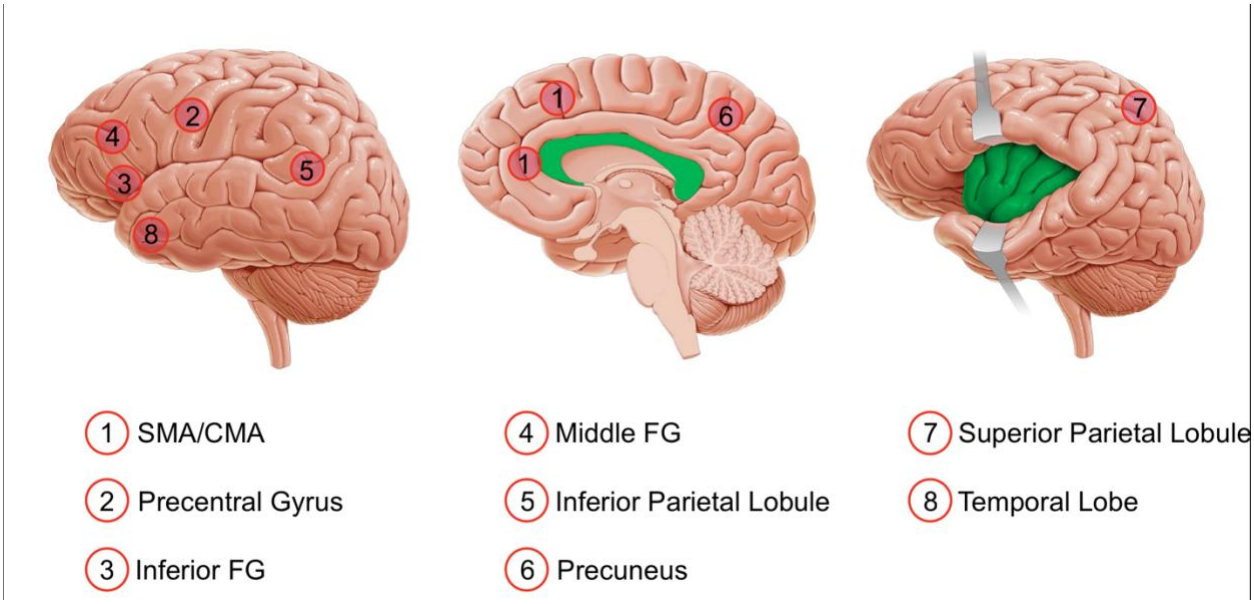


Figure 3: Cerebral regions associated with the encoding phase of the Sternberg task among healthy participants (Cairo et al., 2004). SMA: supplementary motor cortex; CMA: cingulate motor area; FG: frontal gyrus. The unedited brain photos were retrieved from www.KenHub.com (*KenHub.com*, n.d.).

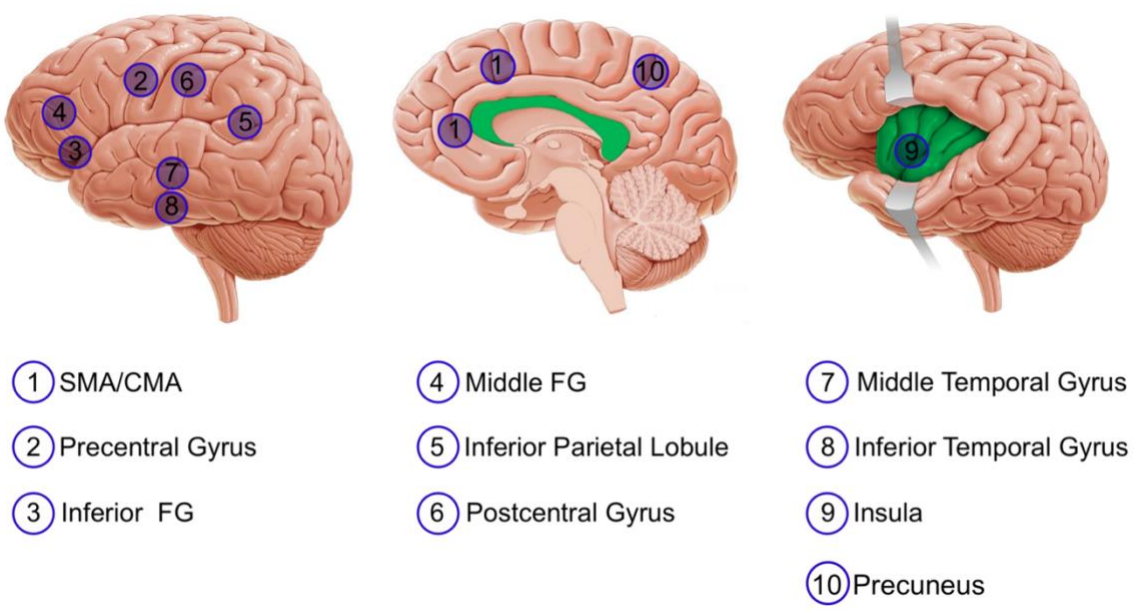


Figure 4: Cerebral regions associated with the recall phase of the Sternberg task among healthy participants (Cairo et al., 2004). SMA: supplementary motor cortex; CMA: cingulate motor area; FG: frontal gyrus. The unedited brain photos were retrieved from www.KenHub.com (*KenHub.com*, n.d.).

1.2.3. Working Memory and Insomnia

A review paper by Shekleton et al. described that patients with chronic primary insomnia tend to have a worse performance on cognitive tasks assessing working memory and attention (Shekleton et al., 2010). Altena and colleagues were among the first researchers to objectively detect cognitive impairment in patients with chronic primary insomnia (Altena et al., 2008). This study, which assessed a group of twenty-five patients (18 females, age: 60.6 ± 6.0 y.o.), showed that the performance of the cohort with insomnia was worse than the control group, in terms of reaction time, for a more complex vigilance task. Since the encoding aspect of working memory is vigilance driven, these findings may have negative working memory-related implications. Another study, that intended to investigate whether hypo-activation of prefrontal regions of the brain translates into objective cognitive impairment, compared the working memory performance of forty-nine elderly patients with primary insomnia (27 females, age: 69.43 ± 4.83 y.o) with forty-nine elderly healthy good sleepers (18 females, age: 70.0 ± 9.31 y.o) using a double span memory task (Lovato et al., 2013). In this task, the participants were required to remember the name and/or spatial location of items in a sequence and the number of items increased with every trial. The study showed that the working memory performance of patients with primary insomnia was comparable to the control group. In contrast, a study by Cellini et al. demonstrated that patients with primary insomnia (13 participants; 8 females, age: 23.31 ± 2.5 y.o) had a lower accuracy rate for non-target trials and higher number of errors compared to healthy good sleepers (13 participants; 6 females, age: 24.31 ± 1.6 y.o) using the 2-back task (Cellini et al., 2014). This was indicative of a worse working memory performance of patients with insomnia compared to the good sleepers. The results were not compared with the core working memory network described earlier. The inconsistent results of these studies may stem from using two different working memory tasks. The reason the N-back task detected an objective difference between the two groups of participants could be due to its higher cognitive load. During the N-back task, participants were required to constantly update and interact with other cognitive domains to manipulate the retained information, whereas the double span task did not require the participants to do any mental manipulation and assessed the recall capability of the participants.

Nonetheless, two recent meta-analyses have described the magnitude of negative impact of insomnia on retention and manipulation phases of working memory as mild to moderate (É. Fortier-Brochu et al., 2012; Wardle-Pinkston et al., 2019). The findings of these meta-analyses are corroborated by another meta-analysis that investigated cognitive deficits in patients with insomnia with a narrower focus (Ballesio et al., 2019). This investigation focuses on three areas of executive function among patients with insomnia: inhibitory control, working memory and cognitive flexibility. Ballesio and

colleagues found that the working memory of patients with insomnia suffer from a lower accuracy compared to healthy participants. Wardle-Pinkston et al. suggested that the manipulation aspect of working memory is potentially more affected by insomnia as it is required to interact with other cognitive domains, such as executive function and episodic memory. Therefore, the negative impact on these cognitive domains can lead to a greater impact on the manipulation phase of working memory (Wardle-Pinkston et al., 2019). These findings increase the likelihood of the scenario that daytime functioning impairment among individuals with insomnia is the result of mild deficits in a few important cognitive domains. To better understand why chronic primary insomnia may affect working memory, we may need to use techniques that allow us to assess the brain function during a working memory paradigm like functional neuroimaging. Such techniques allow us to better understand whether brain function alterations due to insomnia translates into cognitive impairment and why patients with insomnia experience subjective cognitive impairment.

1.3. Insomnia and Functional Neuroimaging

1.3.1. Impact of Insomnia on Regional Brain Activation During a Working Memory Task

Our project uses the Sternberg task which requires the participants to memorize a sequence of digits for a short period of time and decide whether they saw the target among the sequence of digits (further details on the Sternberg task are in the methods section). This task lacks a verbal component and does not require participants to memorize any spatial information. To our knowledge, the Sternberg task has never been used to evaluate the working memory of patients with chronic primary insomnia and only two neuroimaging studies, using fMRI, have used the N-back task , another commonly used task that lacks a verbal component, to assess this cognitive domain among patients with insomnia (Drummond et al., 2013; Son et al., 2018). An advantage of the Sternberg task over these two tasks is its ability to assess different phases of working memory separately. While both studies reported that objective performance of patients with chronic insomnia was comparable to healthy good sleepers, their neuroimaging findings showed group differences. Drummond et al. used a version of the N-back task with three levels of difficulty (i.e. 1-back, 2-back, 3-back) and conducted two different sets of fMRI analyses. First, they assessed whether patients with insomnia (25 subjects; 12 females; age: 32.4 ± 7.1 y.o) had a different cerebral response to an increase in the level of difficulty of the task compared to healthy good sleepers (25 subjects; 12 females; age: 32.3 ± 7.2 y.o). Second, they evaluated whether patients with insomnia use a different set of brain regions, relative to the control group, during the working memory task. They observed that the brain activity of good sleepers in regions of the middle frontal cortex (Brodmann areas 46 and 9) increases as the task gets more challenging. They also observed that certain regions, such as orbital frontal gyrus (Brodmann 11), pregenual cingulate gyrus

(Brodmann 32) and posterior cingulate (Brodmann 23) show greater deactivation in good sleepers. These regions pertain to the default mode network (DMN), a collection of brain regions that are active when the brain is not engaged in a goal-oriented behavior and deactivated when the brain performs active attention-demanding tasks (Andreasen et al., 1995; Buckner & DiNicola, 2019; Shulman et al., 1997). In comparison, they noted that the magnitude of activation of cerebral regions involved in working memory and deactivation of DMN-related regions were not modulated by the difficulty level of the task in patients with insomnia. Also, patients with insomnia experienced a worse subjective performance in comparison with healthy good sleepers which was positively correlated with the lack of deactivation of brain regions associated with the DMN. Moreover, several brain regions associated with the frontoparietal working memory network, premotor areas, visual processing areas and thalamus showed a greater activation in healthy good sleepers compared to patients with insomnia (Owen et al., 2005). In addition, this study identified that the activation of five clusters (bilateral frontal pole, left middle frontal gyrus, left posterior parietal cortex, right cerebellum, left cerebellum) were positively associated with better objective performance regardless of the group of participants. The results of this study suggest that possible abnormalities in the DMN network in patients with insomnia and a lack of increase in activation of task-related brain regions in response to increase in difficulty may contribute to daytime functioning impairment. The second study, conducted by Son et al., did not use subjective measurements of cognitive performance and their neuroimaging findings are inconsistent with the results of the previous study (Son et al., 2018). The working memory task used in this study was the 2-back task. They found that none of the brain regions activated during the task showed less activation in patients with chronic primary insomnia (21 subjects; 12 females; age: 36.6 ± 9.8 y.o) relative to healthy good sleepers (26 subjects; 15 females; age: 36.6 ± 9.8 y.o). However, they observed that the activation in two brain regions (right lateral inferior frontal cortex and right superior temporal pole) were significantly higher in patients with insomnia compared to healthy good sleepers during the task. The investigators used these two cerebral regions for their subsequent analyses. They noted that the activation of interest regions was not correlated with any of the sleep parameters (e.g. total sleep duration) in either groups. However, their regression analyses showed that the total score of the insomnia severity index (ISI; Min = 0; Max = 28) was negatively correlated with brain activation in the right middle temporal cortex for the group of patients with insomnia. Without considering this piece of evidence, Son and colleagues hypothesized that patients with chronic primary insomnia may over-recruit the neural networks involved in their cognitive task as a compensatory strategy to perform as well as healthy good sleepers. Lastly, both studies suggested that the lack of difference between the objectively measured cognitive performance of two groups may be due to low sensitivity of the N-Back

task. It is difficult to compare the neuroimaging of these two studies due to the use of different contrasts and variations of the N-back task.

Another fMRI study that investigated the cerebral activation of patients with primary insomnia during a working memory task used a spatial working memory task (Li et al., 2016). In this particular task, participants had to memorize the location of a dot on a 12-point analog clock face. In this study, the cognitive performance of patients with chronic primary insomnia (30 subjects; 13 females; age: 39.36 ± 8.53 y.o) was significantly worse compared to performance of healthy good sleepers (30 subjects; number of females was not indicated; age: 36.15 ± 8.61 y.o). The neuroimaging findings of this study indicated that the pattern of cerebral activation differ between the two groups of patients with insomnia and healthy good sleepers during this task. The results revealed that the brain regions that were activated during the spatial working memory task in patients with insomnia were bilateral parietal lobes, bilateral frontal lobes, bilateral temporal lobes, bilateral occipital lobes, bilateral insular lobes, left para-hippocampal gyrus, left thalamus and right pons. In contrast, a larger number of cerebral regions were activated in healthy groups during this task. These brain regions included bilateral parietal lobes, bilateral frontal lobes, bilateral temporal lobes, bilateral occipital lobes, bilateral insular lobes, midbrain, thalami and pons. Based on the finding of this study, Li and colleagues suggested that alterations in the cerebral function of patients with chronic primary insomnia can have a negative impact on spatial working memory capacity of this population.

Study	Technique	Working Memory Task	N (female)		Age (SD), (years)		Main findings
			PI	HGS	PI	HGS	
Drummond et al., 2013	fMRI	N-back(4 difficulty levels; N= {0,1,2,3}	25(12)	25(12)	32.4 ± 7.1	32.3 ± 7.2	Comparable working memory performance between groups. Cerebral activation in PI is not modulated by level of difficulty and related regions to the working memory task showed higher levels of activation in HGS.
Li et al., 2016	fMRI	Spatial working memory	30(13)	30(not disclosed)	39.36 ± 8.5	36.15 ± 8.6	Spatial working memory of PI was significantly worse than performance of HGS. A larger number of cerebral regions were activated in HGS.
Son et al., 2018	fMRI	2-back	21(12)	26(15)	36.6 ± 9.8	36.6 ± 9.8	Comparable working memory performance between groups. Two specific cerebral regions showed higher activation in PI: right lateral inferior frontal cortex and right superior temporal lobe.

Table1: Summary of three neuroimaging studies investigating the brain function of patients with chronic primary insomnia during a working memory task. PI: Patients with insomnia, HGS: Healthy good sleepers.

Study	Comment	Brain regions	Coordinates			BA
			X	Y	Z	
Drummond et al., 2013	These regions were activated in PI during working memory, but their level of activation or deactivation was not modulated by increase in difficulty level of working memory task. MNI coordinates were used.	Right middle frontal gyrus	45.3	39.4	20.9	46
		Right middle frontal gyrus	47.2	28.6	34.4	9
		Left pregenual cingulate cortex	-4.3	33.2	17.4	32
		Bilateral posterior cingulate cortex	3.7	-52.8	23.8	23
		Left orbital frontal gyrus	-2.1	38.9	-16.6	11
Li et al., 2016	Brain regions with highest level of activation during working memory task. Authors did not precise whether these regions showed greater levels of activation compared to the control group. MNI coordinates were used.	Left inferior temporal gyrus/middle temporal gyrus	-39	9	-45	20
		Left superior temporal gyrus	-36	12	-39	11
		Left middle temporal gyrus	-57	-36	-3	14
		Left occipital lobe/cuneus	-24	-81	27	18
		Right anterior central gyrus/middle frontal gyrus	54	-9	51	11
Son et al., 2018	This study only indicated the two regions that were significantly more activated in PI during working memory. MNI coordinates were used.	Right lateral inferior frontal cortex	51	27	-6	47
		Right superior temporal pole	57	9	-15	38

Table 2: Regions that were activated during working memory task in patients with primary insomnia in previous neuroimaging studies. PI: Patients with insomnia, BA: Brodmann's Area, R: Right cerebral hemisphere, L: Left cerebral hemisphere, A: Anterior, P: Posterior, S: Superior, I: Inferior.

1.3. Knowledge Gap and Current Study

Current literature suggests two possible mechanisms as to why insomnia impacts working memory objectively and/or subjectively (Drummond et al., 2013; É. Fortier-Brochu et al., 2012; Kay et al., 2016; Nofzinger et al., 2004; O'Byrne et al., 2014; Son et al., 2018; Wardle-Pinkston et al., 2019). Evidence suggests that metabolism of cognitive related regions is altered in patients with insomnia during cognitive abilities assessment. The second potential reason affecting the cognitive capacity of patients with insomnia is the activation of non-working memory task-related regions in patients with insomnia during cognitive-demanding tasks. Moreover, the worse subjective cognitive performance is also correlated with this alteration. It is hypothesized that physiological factors associated with pathology of insomnia, like hyperarousal, contributes to this cerebral metabolism alteration. However, currently, it is unclear which one of these mechanisms, or whether a combination of both, lead to objective and/or subjective working memory impairment among patients with chronic primary insomnia. Previous studies demonstrated that the activation of regions that can play an important role in working memory is altered among our population of interest, providing support for the first mechanism. Yet, these findings were not replicated constantly and there are studies contradicting these findings as it was mentioned earlier. The source of this inconsistency may be attributed to variability in cognitive loads of different working memory paradigms in research and variability in severity of insomnia of participants. Hence, this inconsistency in the literature grants further investigation of the impact of chronic primary insomnia on different phases of working memory using the Sternberg task to provide more nuance on the effect of this disorder on cerebral function during cognitive assessment. Albeit the current study is a small part of an ongoing longitudinal project that thoroughly investigates the impact of cognitive behavioural therapy for insomnia on the function of the brain. This includes, but not limited to, the functional connectivity and morphology of brain using a larger a sample size. Additionally, our larger longitudinal project attempts to investigate neuroimaging biomarkers of response to cognitive behavioural therapy for insomnia. It is important to note, the objective of the current project is limited to examining a potential anatomical pattern of activity in different phases of working memory in patients with chronic primary insomnia. Anything related to functional connectivity is beyond the scope of this thesis study.

1.4. Research Objectives

Our study aims to investigate the brain function of patients with chronic primary insomnia during the Sternberg task, a working memory paradigm that has never been used to assess the working memory of these patients. We chose this working memory paradigm because it enables us to evaluate

two aspects of working memory separately (i.e. encoding and retrieval) and to assess whether the brain activation changes as the difficulty of the task increases. More precisely, in this study, we aim to conduct a preliminary analysis to identify activated cerebral regions in response to the Sternberg task in patients with chronic primary insomnia. To our knowledge, this is the first study employing the Sternberg task to evaluate working memory capacity of patients with chronic primary insomnia. In line with previous insomnia studies, we expect to observe a different set of brain regions to be activated in response to the Sternberg task among participants with insomnia compared to regions reported in healthy individuals. Additionally, we anticipate to observe a decrease in working memory performance of participants with insomnia in response to an increase in cognitive load of our task.

2. Method

2.1. Study Design and Participants

Our study aimed to recruit and match ten participants with chronic primary insomnia and ten healthy good sleepers based on age, sex and level of education. However, due to unforeseen circumstances surrounding the COVID-19 pandemic and strict governmental regulations for non-essential research studies involving humans, we were unable to have a control cohort. We acknowledge that a lack of a control group is a major limitation to this study, and this will be addressed thoroughly in the discussion section.

Our project is a cross-sectional study that is a part of a larger longitudinal study investigating the potential of neuroimaging in predicting the biomarkers for response to cognitive-behavioural therapy for insomnia. For the purpose of this project, we specifically used the fMRI data that was collected during the first visit of participants following eligibility screening and prior to the start of the cognitive behavioural therapy intervention. All eligible participants had to be between 25 and 65 years old. Participants with insomnia had to fit the diagnostic criteria for chronic primary insomnia established by the DSM-V. The diagnostic criteria are as follows: 1) sleep latency greater than 30 minutes 2) wake after sleep onset greater than 30 minutes and/or 3) waking up earlier than desired by at least 30 minutes. These symptoms, that are subjective in nature, must be present with subjective daytime functioning impairment and occur at least three times per week for three months to be diagnosed with insomnia (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013). In addition, they should not have any other neurological, psychological or psychiatric disorders that can affect their sleep or cognitive performance. Specifically, the exclusion criteria are:

1) epilepsy with seizure in the past year or in lifetime

2) concussion in the past 3 months, concussion followed by loss of consciousness or multiple concussions in lifetime

3) multiple sclerosis

4) Parkinson's disease

5) past severe traumatic brain injury

6) past history of brain lesion

7) major surgery requiring general anesthesia in the past three months

8) untreated thyroid disorder

9) chronic pain syndrome self-reported as interfering with sleep

10) recent severe infection in the past three months

11) active cancer or treated cancer with post-cancer treatment for less than two years

12) major cardiovascular events or intervention history

13) sleep apnea with an apnea-hypopnea index of greater than five per hour and restless leg syndrome with symptoms three days or more per week, Or any chronic obstructive and restrictive pulmonary disease that can affect the overall health of participants.

14) periodic limb movement during sleep with an index of greater than fifteen per hour

15) rapid eye movement-sleep behaviour disorder with more than one episode per month 16) narcolepsy with cataplexy

17) having worked night shifts for more than two weeks in the last 3 moths

18) diagnosed dementia

19) severe mental disorder, such as psychotic disorders, anxiety disorder or major depression

20) hypomania

21) cyclothymic

22) consumption of more than ten glasses of alcohol per week

23) use of cannabis more than once a month

24) smoking more than ten cigarettes per day

25) breastfeeding, pregnant or planning to get pregnant

26) currently participating in a psychotherapy or use of medication for depression or anxiety as they can alter function of certain regions of the brain (Horga et al., 2014).

27) Inability to undergo an MRI scan due to metallic implant or claustrophobia.

The screening process of participants went through three stages. The first step consisted of a 30-minute phone interview with one of our research assistants. In this stage, the potential candidates were asked a list of questions concerning their sleep habits and sleep disorders, medical history and

psychological health history. In the second stage of the screening process, potential participants underwent a medical interview and a structured clinical interview for DSM-V, which was used for the diagnosis of insomnia, depression, anxiety and other psychiatric disorders. During the interview, which was conducted by a trained individual, participants were asked to provide a more extensive medical and psychological history. Subsequently, eligible participants were invited for a polysomnography (PSG) night at our sleep laboratory located at the PERFORM Centre. During the PSG night, participants stayed overnight at the lab, and we measured their brain electrical activity (EEG), heart electrical activity (electrocardiography; ECG), eye movements (electro-oculography; EOG), muscle movements (electromyography; EMG) of maxillofacial region and legs, breathing rate and blood oxygen saturation. The primary purpose of this night was to confirm that our participants did not have other sleep disorders. It also served as a habituation night for the subsequent visits. Once their eligibility was confirmed after the PSG night, we invited the retained participants to come back to our sleep laboratory for an MRI scan. The MRI scan took place at the imaging suite of the PERFORM Centre two weeks after the PSG night (these procedures are explained further in section 2.2).

The protocol for this project was approved by the *Comité Central d'Éthique de la Recherche* of the *Ministère de la Santé et des Services Sociaux* and all participants signed an informed consent document prior to the start of their involvement in this study.

2.2. Data Collection

2.2.1. Pre- and Post-MRI Scan Procedure

On the day of the MRI scan and EEG recording night participants were required to arrive at our sleep laboratory between 3 PM and 4 PM. Once the participants were ready, we explained to the participants four tasks that they were required to perform in the MRI scanner. They also had a chance to perform a few practice trials. The participants were asked to do one practice run, however, they were able to request to for additional practice trials. The four tasks included a resting state task, a working memory task (i.e. the Sternberg), an emotional reactivity task and a declarative memory task (i.e. face-name task). We explained the tasks prior to the MRI scan to ensure that the participants understood them correctly. We also wanted to limit the amount of time the participants had to spend in the scanner.

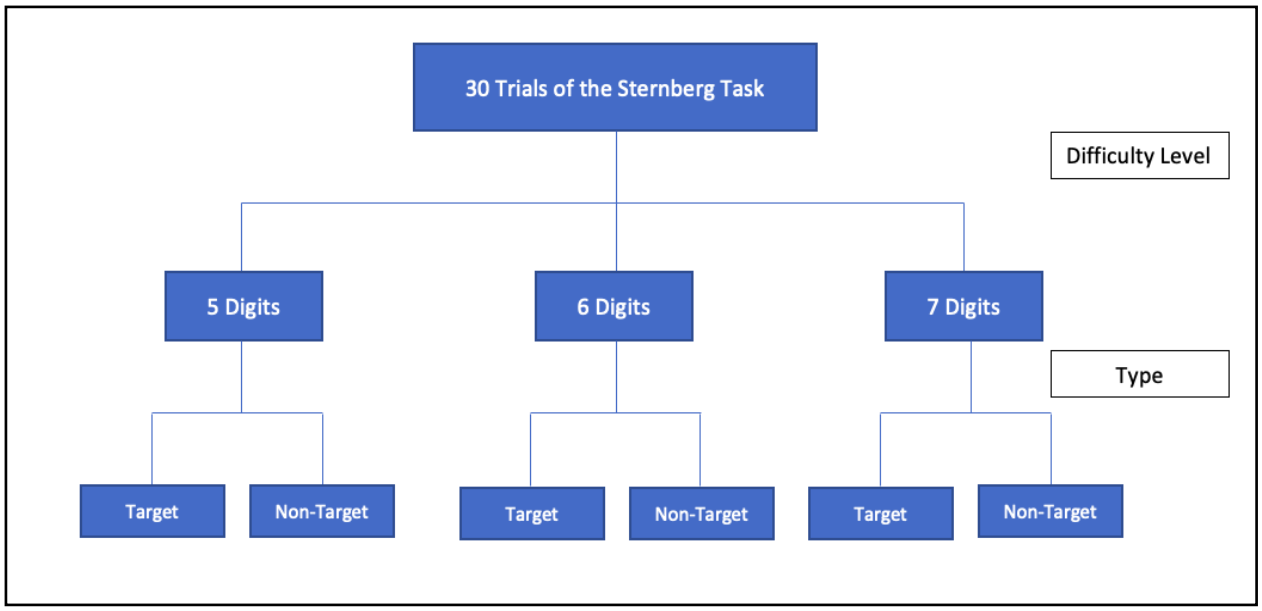
After the MRI scan, participants returned to the sleep lab, and a sleep technologist with the help of a research assistant applied the EEG gold cup electrodes on their scalp according to the 10-20 international system. The brain's electrical activity is recorded using 17 scalp EEG electrodes. Similar to the PSG night, we also recorded their heart's electrical activity (ECG), eyes movement (EOG) as well as muscle movement of maxillofacial region (EMG). All recordings were sampled at 512 Hz with a band-pass filter between 0.3 and 100 Hz (SOMNOMedics, Germany). Before going to bed,

participants were given an actigraphy that records their sleep pattern for a period of two weeks. They were also instructed to complete a sleep diary every day for the next two weeks. Sleep diaries were used to complement the actigraphy data. Lastly, the sleep recording lasted throughout night and participants left the following day after performing a set of cognitive tasks and saliva collection. An overview of the pre- and post-MRI scan procedure can be seen on figure 6.

2.2.2. Working Memory Paradigm

The working memory paradigm used in this study was the Sternberg task (Figure 5). During the task, participants saw a series of digits one after the other one over a span of 10.5 seconds. Two to four seconds after the sequence of digits was over, participants were shown a digit (i.e. target or non-target) and were asked whether they saw this particular digit among the sequence of digits that they were just shown. Then, participants had to either answer yes by using their index finger to press a button on the response box (figure 7), or answer no by using their middle finger to press a button on the response box. The Sternberg task lasted 11 minutes and 20 seconds and the participants complete thirty trials during this time. Every trial was divided into two sections of encoding (i.e. memorizing the series of digits), which lasted 10.5 seconds, and retrieval (i.e. responding to the target), which lasted 3.5 seconds. There was also a fixation period between the two phases lasting between two to four seconds. Moreover, all of the trials were equally distributed into three categories of difficulty (i.e. ten trials per level of difficulty). The number of digits shown in the encoding section of every trial determined the level of difficulty of the trial, which varied from five to seven digits. As a result, the lowest level of difficulty included five digits, the middle level of difficulty included six digits and the highest level of difficulty included seven digits in the series of digits shown to the participants. Hereinafter, these levels were referred to as the easiest difficulty level, the medium difficulty level and the highest difficulty level, respectively. Lastly, the trials in every difficulty level were equally divided into two types of target and non-target trials (i.e. 5 target trials and 5 non-target trials for each difficulty level). Target trials were those that included the stimulus in the encoding section and the non-target trials were those that did not include the stimulus in the encoding section. Target and non-target trials were not analyzed separately for this project, but they are mentioned here to provide as much information as possible regarding the nuance of our task. Conditions were presented in a random manner.

A)



B)

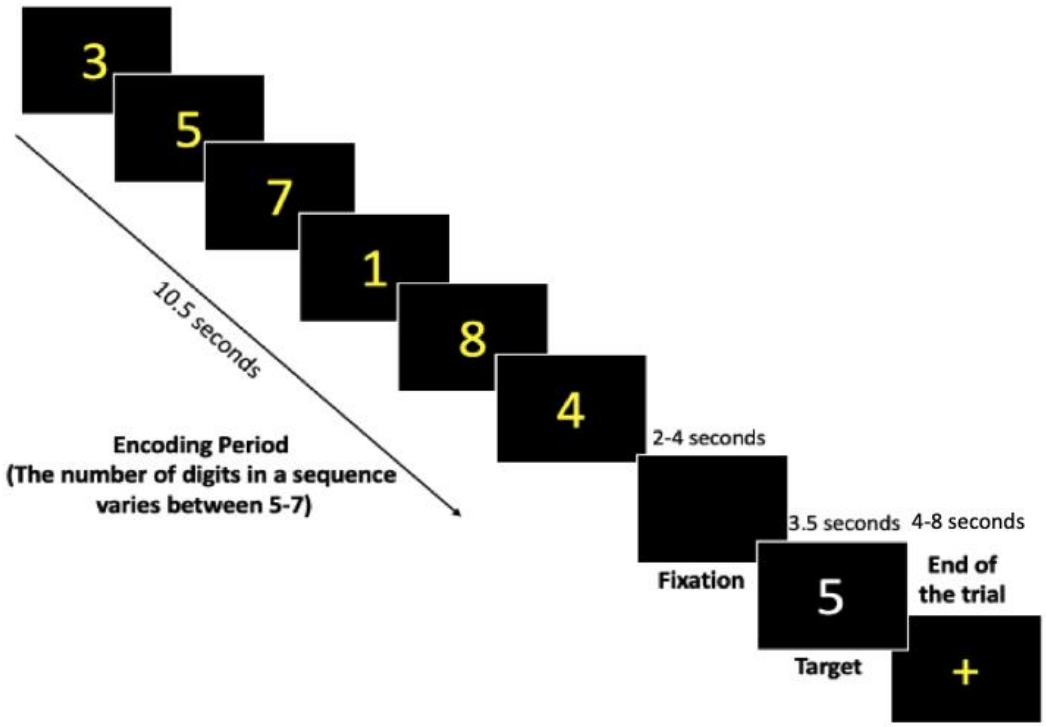


Figure 5: A) A diagram outlining the breakdown of the Sternberg task trials in terms of difficulty levels and target Vs. non-target. B) A Schematic overview of the Sternberg task.

2.2.3. Scanning Procedure

The MRI session was performed in a 3T General Electric scanner with a 32-channel head coil. During the scan, the participants were required to perform the four tasks. The time for every task ranged from 7 to 13 minutes. In the scanner, the participants were able to see the tasks via a mirror fixed on the head coil.

During each scan session, we acquired a set of anatomical images (T1, T2 and diffusion as well as magnetic resonance spectroscopy) of the brain and a set of functional images which were taken during the tasks. Anatomical scans used a T1-weighted BRAVO sequence (Repetition Time = 7908 ms, Echo Time=3.06 ms, Field of view = 25.6, flip angle = 12 degrees, frequency direction = anterior to posterior, image matrix = 256 x256, resolution 1x1x1mm). The functional scans were sensitive to the T2* blood-oxygenation-level-dependent (BOLD) signal, and 370 gradient echo, echo planar images were collected across 41 axial slices covering the whole brain (Repetition Time = 2500 ms, Echo Time=26 ms, field of view = 25.6, flip angle = 77 degrees, frequency direction = right to left, image matrix = 64 x 64, resolution = 4 x 4 x 4 mm).

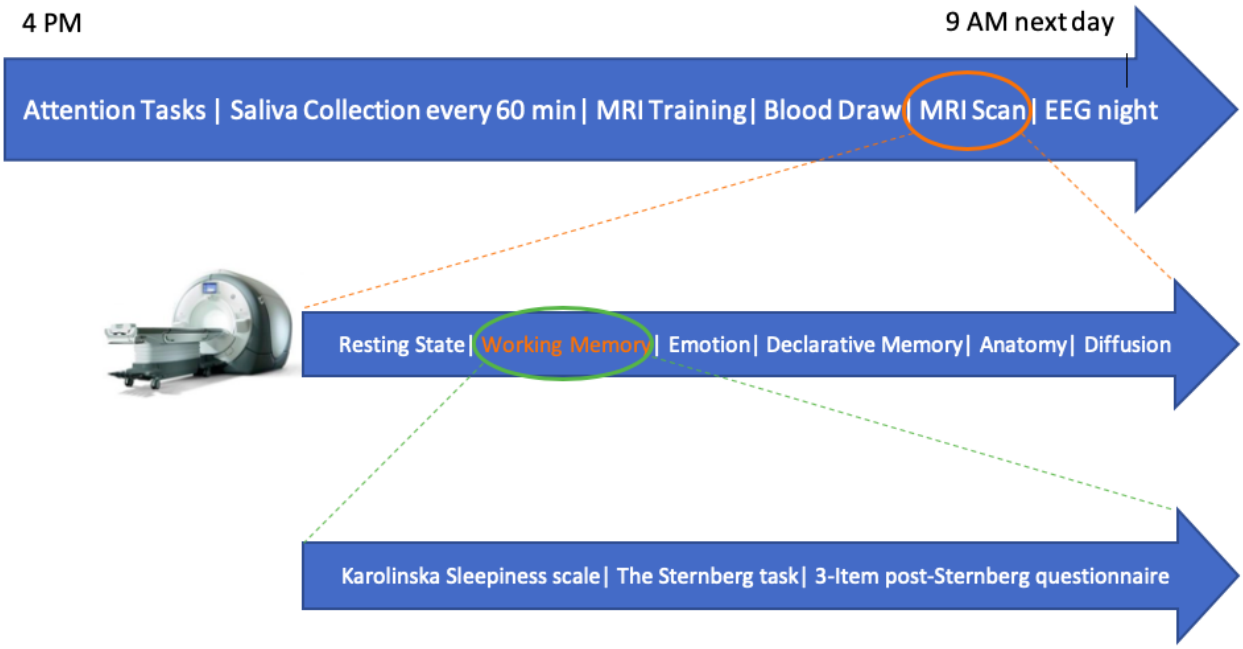


Figure 6: Overview of the pre-MRI scan procedure and the tasks and scans performed during the MRI session.

Figure 7: The response box used in the MRI scanner to interact with the tasks displayed on the mirror.

2.2.4. Subjective Questionnaires

In this project, we used four different subjective questionnaires: insomnia severity index (ISI), Beck's depression inventory (BDI), Karolinska sleepiness scale (KSS) and 3-item post Sternberg questionnaire. The goal was to evaluate the severity of insomnia, severity of depressive symptoms, level of sleepiness prior to the task and level of motivation as well as the perception of difficulty and subjective performance. For the purpose of exploratory analyses, we intended to assess the association of these variables with working memory performance.

ISI: A study by Fortier-Brochu and Morin showed that individuals who indicated that they experience subjective cognitive deficit on the ISI scale have a worse memory and attention performance (E. Fortier-Brochu & Morin, 2014). Their clinically validated questionnaire, which is a tool used to monitor treatment outcomes of the patients, subjectively assesses and quantifies the severity of insomnia in these individuals (Bastien et al., 2001). ISI was administered during the screening phase of the study. It is a seven-item questionnaire that asks patients to rate how severe their insomnia symptoms were, how much it interfered with their daily life and cognitive functioning and how much their sleep pattern affected their stress level on a five-point Likert scale (0=Not all, 4= Extremely). A higher total score on the ISI signifies that their condition was more severe (minimum total score=0; maximum total score=28).

BDI: This questionnaire, administered during the screening phase of the study, contains twenty-one questions assessing the severity of depressive symptoms of the participants (Beck et al., 1961). A higher score on the BDI questionnaire indicates more severe depressive symptoms (minimum total score = 0; maximum total score = 63). We assessed the correlation of depressive symptoms with working memory performance since insomnia and depression are comorbid conditions and there is evidence that depressive symptoms alone could affect memory functioning (Kizilbash et al., 2002; Morin & Jarrin, 2013).

KSS: This is a subjective questionnaire that measures the level of sleepiness of a participant at a particular point in time (Akerstedt & Gillberg, 1990). It evaluated the level of sleepiness of the participants based on their feeling over the past five minutes on a scale of one to nine (1= extremely alert, 9= extremely sleepy). The KSS score has been shown to be highly correlated with EEG and behavioural measures (Kaida et al., 2006). In this study, we used KSS at different points in time to measure the sleepiness of the participants. However, for the purpose of this project, we only used the KSS score that was obtained right before the performance of the Sternberg task in the MRI scanner. This was done to assess whether the alertness of participants before the task was associated with their working memory performance.

3-item post Sternberg questionnaire: Literature has linked insomnia with misperception of sleep time and exaggerated perception of stimuli (Baglioni et al., 2014; Harvey & Tang, 2012; Huang et al., 2012). Patients with insomnia who believe insomnia has a greater impact on their cognitive abilities tend to have a poorer cognitive performance (E. Fortier-Brochu & Morin, 2014). Furthermore, a worse subjective cognitive performance may be correlated with higher activation of certain regions of the brain (DMN) during the task (Drummond et al., 2013). The questionnaire (figure 6), created by our team, measured the subjective performance of the participants on the Sternberg task, evaluated how they perceived the difficulty of the task and quantified their level of motivation during the task. This is not a validated questionnaire, and it was the first time that it was used in a neuroimaging study. Immediately after the Sternberg task, the participants completed the questionnaire below while in the MRI scanner (figure 6). They were asked to rate the aforementioned items individually on a scale of one to ten (Performance: 1=Extremely poor, 10=Excellent; Difficulty: 1=Extremely easy, 10=Extremely difficult, Motivation: Extremely unmotivated, 10=Extremely motivated). We formulated the questions as follows:

"1. On a scale of 1 to 10, how well do you believe you PERFORMED on this task?"

"2. On a scale of 1 to 10, how DIFFICULT did you find the task?"

"3. On a scale of 1 to 10, how MOTIVATED were you during the task?"

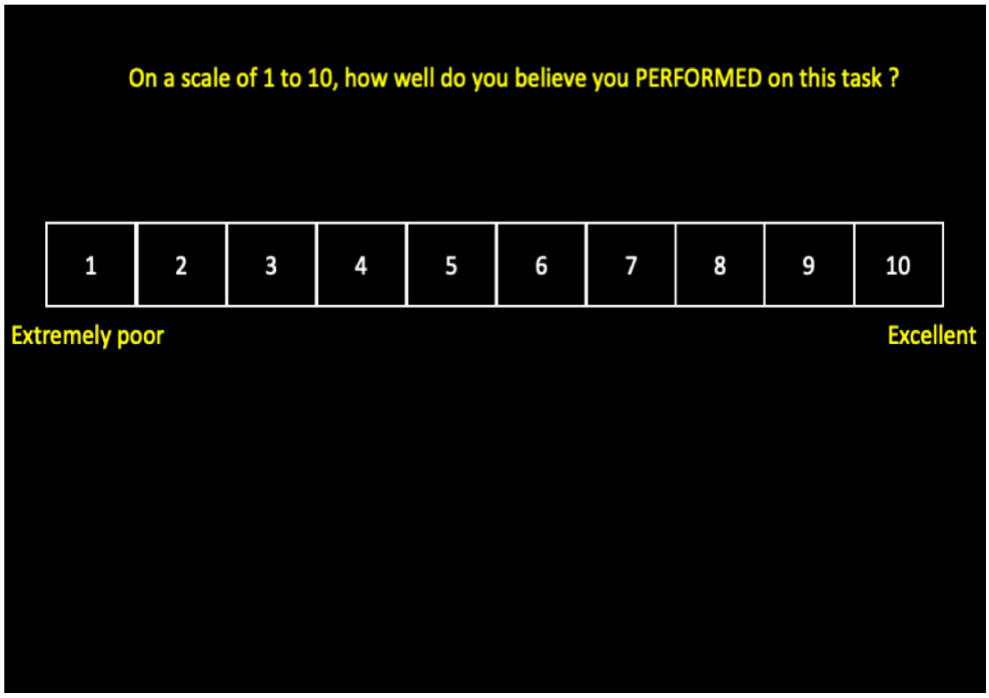


Figure 8: Example of one of the three questions included in our 3-item post Sternberg questionnaire.

2.3. Analyses and Statistics

2.3.1. Working Memory Data

To objectively assess the working memory performance of the participants, we used the overall mean reaction time of the correct answers, the overall percentage of the correct answers, the mean reaction time of correct answers for every difficulty level as well as the percentage of the correct answers for every level of difficulty on the Sternberg task. Considering the small sample size of data, we intended to use the Mann-Whitney test to compare the performance of patients with insomnia and healthy good sleepers on the Sternberg task with a significant level of 0.05. However, due to the lack of a control group this was not done. In addition, we intended to perform Spearman's correlation to evaluate whether the subjective performance and perception of task difficulty were correlated with the objective performance of the participants within groups across different difficulty levels. Likewise, this was not done. The reason we did not perform this correlation was because of the small sample size at our availability. We did, however, perform a Spearman's correlation between ISI and objective working memory performance. Lastly, we used the Kruskal-Wallis test, a non-parametric equivalent of the one-way ANOVA, to examine the effect of working memory load (i.e. level of difficulty) on the performance of subjects within a group.

2.3.2. Preprocessing of fMRI Data

The acquired fMRI data underwent a few steps of preprocessing before it could be used for the analyses. First, the MRI data from the scanner was checked visually to ensure that there were no missing volumes or artifact and excessive head movement using Mango neuroimaging viewer software (Lancaster, Martinez; www.ric.uthscca.edu/mango). Subsequently, the fMRI files were preprocessed (one step of temporal processing and four steps of spatial processing) for further analyses. These five steps were slice-time correction, motion correction, co-registration, normalization and spatial smoothing (Friston, 2003). Preprocessing steps, first-level analysis and second-level analysis were carried out using Statistical Parametric Mapping 12 software (SPM12; Friston; www.fil.ion.ucl.ac.uk/spm)

Slice-time correction: During the Sternberg task, we acquired 270 scans of the whole brain (brain volume) at a 2500 ms interval. Each one of these full brain scans was also made up of 41 axial slices of the brain. The brain scans were obtained at about a 60 ms interval. The slices that created a brain volume were temporally misaligned from each other. So, the purpose of this step was to combine the temporal information of all 41 slices and interpolate this information to a reference time-point. The reference time-point we used is the slice that was obtained half-way through each full brain scan.

Motion correction: The brain volumes are made up of thousands of voxels (three-dimensional cubes with dimensions of 4 mm by 4 mm by 4 mm). Each one of these voxels is associated with a specific coordinate or specific part of the brain structure. However, there is always some degree of head movement in the scanner and since multiple volumes are obtained throughout the task, the spatial information of the voxels in the first volume can be changed across the subsequent volumes. Therefore, the purpose of this step is to ensure that the corresponding spatial information of each voxels that makes up the three-dimension image of the brain, does not change throughout the scan.

Co-registration: Each slice that made up one of the 270 scans during the Sternberg task only gave us information about the regional activity of one part of the brain. Also, the resolution of the functional scans (4 mm x 4 mm x 4 mm) was lower compared to the resolution of the anatomical scans (1 mm x 1 mm x 1 mm). The purpose of co-registration was to project cerebral activation in response to the Sternberg task onto anatomical images (high resolution) of the same participant to create a cerebral activation map with a better quality.

Normalization: The size and anatomy of brain differ between individuals. As a result, voxels with the same coordinate may be associated with different regions of the brain in different individuals. So, the purpose of normalization is to resize the brain by placing it in a standardized space (MNI Space). This way, the voxels with a same coordinate are associated with a specific brain region across the participants, allowing us to compare activation of a brain region between participants.

Smoothing: Although the normalization step adjusted the volume and the size of all the brains to maximize similarity, there were still minor anatomical differences between the brain of participants. As a result, there was a minority of voxels with the same coordinates that did not correspond to the same brain regions across the participants. Smoothing compensated for the remaining individual differences from normalization and increased signal-to-noise ratio.

2.3.3. Within-subject (First Level) Analysis

In the first-level of fMRI data analysis, we used statistical inference in the context of generalized linear model. For this, we included all of the trials of the Sternberg task and controlled for the head movement in six directions (regressors) in the scanner. This was done to localize the cerebral activation within each participant based on the BOLD response (Friston, 2003). The Sternberg task used an event-related design. We established a total of ten contrasts to assess the brain activation for each level of difficulty, each phase and in response to an increase in difficulty of the task (see table 3). Six contrasts compared the intensity of the BOLD response in each phase of working memory (i.e. encoding and recall) in each level of difficulty to the baseline (fixation cross prior to start of trial). Two

contrasts compared the intensity of the BOLD signal in response to the Sternberg task across all difficulty levels, for each phase, to the baseline. Baseline was defined as the period when the fixation cross was shown prior to the start of trial. During this period, participants were not cognitively engaged. The remaining contrasts gave us information regarding the change of the BOLD signal in response to the increase in difficulty level of the working memory task. These contrasts evaluated the change in the intensity of BOLD signal in response to the increase in difficulty level compared each phase of working memory in the highest level of difficulty to the lowest level of difficulty.

During our working memory task, we conducted one-sample t-test (thresholded at $p<0.001$ uncorrected) to detect both activated and deactivated regions for each contrast (see table 4). We used age and sex as covariates for this analysis. Lastly, we used a mask to exclude any signals outside of the brain.

Contrast	Purpose
Encoding phase in the lowest difficulty level Vs. Baseline	Assessment of brain activation in the easiest level.
Recall phase in the lowest difficulty level Vs. Baseline	Assessment of brain activation in the easiest level.
Encoding phase in the medium difficulty level Vs. Baseline	Assessment of brain activation in the middle level.
Recall phase in the medium difficulty level Vs. Baseline	Assessment of brain activation in the middle level.
Encoding highest difficulty level Vs. Baseline	Assessment of brain activation in the hardest level.
Recall highest difficulty level Vs. Baseline	Assessment of brain activation in the hardest level.
Encoding all levels of difficulty Vs. Baseline	Assessment of brain activation for each phase.
Recall all level of difficulty Vs. Baseline	Assessment of brain activation for each phase.
Encoding lowest difficulty level Vs. Encoding highest difficulty level	Assessment of the effect of increase in difficulty during the encoding phase
Recall lowest difficulty level Vs. recall highest difficulty level	Assessment of the effect of increase in difficulty during the recall phase

Table 3: Overview of all the contrasts established to investigate the effect of group and effect of increase in difficulty of task on the pattern of brain activation.

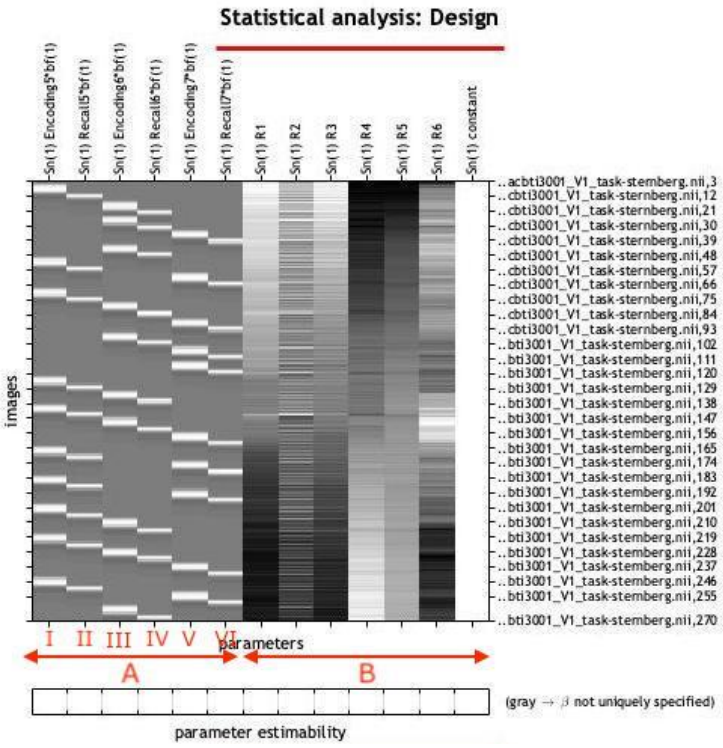


Figure 9: An overview of our statistical design for the first-level analysis. **A)** Six of ten contrasts used to assess the brain activation during each phase of working memory by difficulty level. White areas correspond to the duration of the condition of interest. AI) The encoding period of first level of difficulty. AII) The retrieval period of first level of difficulty. AIII) The encoding period of second level of difficulty. AIV) The retrieval period of second level of difficulty. AV) The encoding period of third level of difficulty. AVI) The retrieval period of third level of difficulty **B)** Head motion in different directions that are being used the control parameters.

2.3.4. Between-subject (Second Level) Analysis

In the final stage of the fMRI data analysis, we conducted two sets of statistical analyses. Initially, we performed a one-sample T-test to determine the cerebral regions that were activated or deactivated during the Sternberg task for patients with insomnia. Then, we performed multiple regressions to assess the correlation our regions of interest, during encoding and recall phases of the task and performance during the Sternberg task. Activation is defined as higher levels of activation within a region compared to the determined baseline and deactivation means lower levels of activation withing a region compared to the selected baseline. Performance was measured as the accuracy percentage and average reaction time of the correct trials during the Sternberg task. The selected regions of interest outlined below were chosen based on their relevance to working memory. We used age and sex as covariates for all sets of statistical analyses. To be consistent with a previous fMRI study that investigated the working memory performance of patients with chronic primary insomnia, we only included the clusters that were larger than 50 voxels in our results table. Statistical threshold was set at 0.05 for the peak clusters. While we did not use multiple comparisons, due to our low number of participants, we acknowledge that its use is important to decrease the probability of type 1 error.

We selected three bilateral regions of interest for each phase of the Sternberg task based on the findings of the previous fMRI studies that used the Sternberg task in healthy participants and a coordinate-based meta-analysis of 189 neuroimaging studies (Cairo et al., 2004; Rottschy et al., 2012). Some of the selected regions were not part of the reported core network working memory by Rottschy et al. This includes the cingulate gyrus and superior parietal lobe. The selected regions for the encoding phase were bilateral cingulate gyrus, bilateral superior parietal lobule and bilateral inferior gyrus. The regions for the recall phase were bilateral middle frontal gyrus and bilateral inferior frontal gyrus and bilateral anterior insula.

The coordinates of our regions of interest were selected based on one of the first fMRI studies that delineated a pattern of activation associated with each phase of the Sternberg task in healthy individuals (Cairo et al., 2004). Cairo and colleagues reported their results using the Talairach coordinates. We used the Bioimage Suite Web, a Java applet at Yale university, to convert the Talairach coordinates to the MNI coordinates (Lacadie et al., 2008). In instances where the regions of interest were not activated bilaterally, we selected the coordinates of the same regions on the opposite hemisphere by changing the sign of the x coordinate (e.g. $x = -4 \rightarrow x = 4$). The coordinates of our regions of interest can be found in the tables below (tables 4 and 5).

ROI	Coordinates		
	X	Y	Z
L. Cingulate Gyrus	-13	-2	62
R. Cingulate Gyrus	13	-2	62
L. Superior Parietal Lobule	-15	-73	58
R. Superior Parietal Lobule	15	-73	58
L. Inferior Frontal Gyrus	-56	6	17
R. Inferior Frontal Gyrus	56	6	25

Table 4: Coordinates of Regions of Interest for the Encoding Phase of the Sternberg Task (Cairo et al., 2004).

ROI	Coordinates		
	X	Y	Z
L. Middle Frontal Gyrus	-33	53	17
R. Middle Frontal Gyrus	33	53	17
L. Inferior Frontal Gyrus	41	32	24
R. Inferior Frontal Gyrus	-41	32	24
L. Anterior Insula	-37	25	-13
R. Anterior Insula	32	30	-9

Table 5: Coordinates of Regions of Interest for the Recall Phase of the Sternberg Task (Cairo et al., 2004).

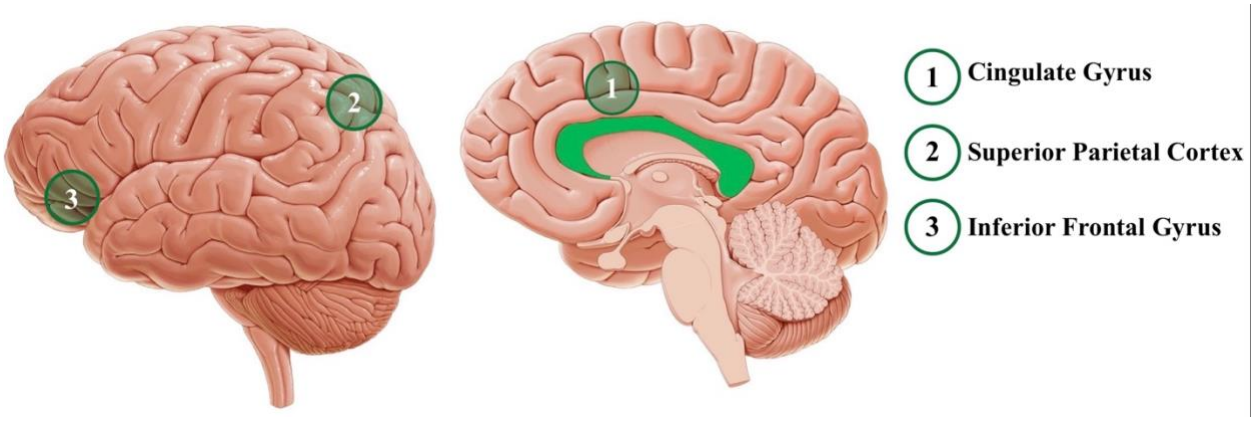


Figure 10: Schematic of the regions of interest for the encoding phase (Cairo et al., 2004). The unedited brain photos were retrieved from www.KenHub.com (*KenHub.com*, n.d.).

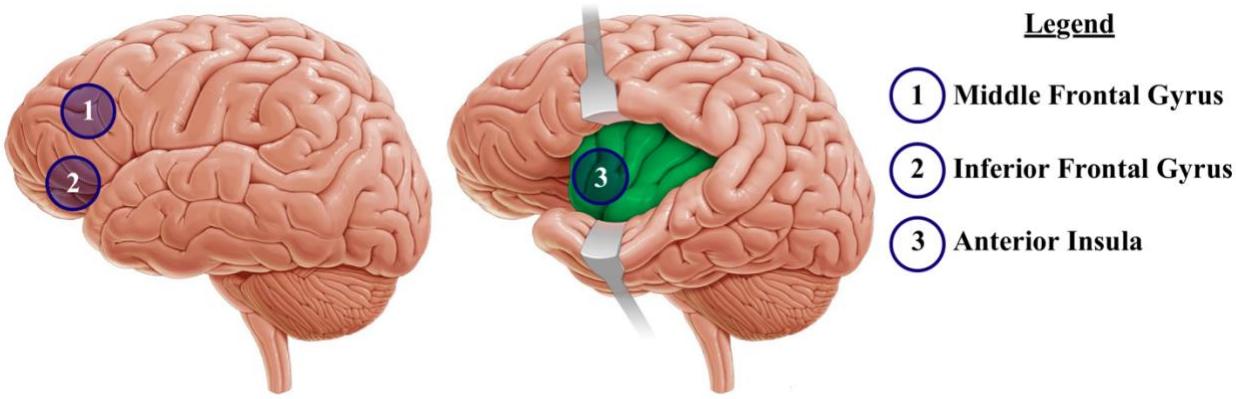


Figure 11: Schematic of the regions of interest for the recall phase (Cairo et al., 2004). The unedited brain photos were retrieved from www.KenHub.com (*KenHub.com*, n.d.).

3. Results

3.1. Demographic and Clinical Characteristics of the participants

A total of nine eligible subjects with primary chronic insomnia (6 females, Age: 49.8 ± 14.06) were included in the analysis. Of these participants, six were Caucasians, one participant was Middle Eastern, one was Latin American, and one was from mixed background. In terms of level of education, three participants obtained their master's degree, four participants obtained their bachelor's degree and the highest level of education of the remaining two participants were CEGEP and high school diploma. On average, the participants rated their subjective performance (4±2.97) on the lower end of the scale and their perception of the task difficulty and level motivation hovered around the middle of the scale (perception of difficulty: 5.34±2.34; level of motivation: 5.16±3.31). Average ISI score of the participants fell in the clinical range (moderate severity; 16.23±3.87) and their mean BDI score (9.34±6.04) ranged from minimal to mild depression. Four out of the nine participants fell in the range of mild depression. In addition, average level of alertness of patients with insomnia was recorded as alert (3.78±1.47) The summary of demographic information and other clinical characteristics can be found in table 5. We lacked a control group due to the challenges imposed on human trials by the COVID-19 pandemic.

Variable	Subjects with Primary Chronic Insomnia
N	9 (6 females)
Age (years old)	49±14.06
Ethnicity	White: 6 Middle Eastern: 1 Latin American: 1 Mixed: 1
Level of Education	Master's degree: 3 Bachelor's degree: 4 CEGEP: 1 High School graduate: 1
Subjective Performance (out of 10)	4±2.97
Perceived Level of Difficulty (out of 10)	5.34±2.34
Level of Motivation (out of 10)	5.16±3.31
ISI (out of 28)	16.23±3.87
BDI (Out of 63)	9.34±6.04
KSS (Out of 9)	3.78±1.47

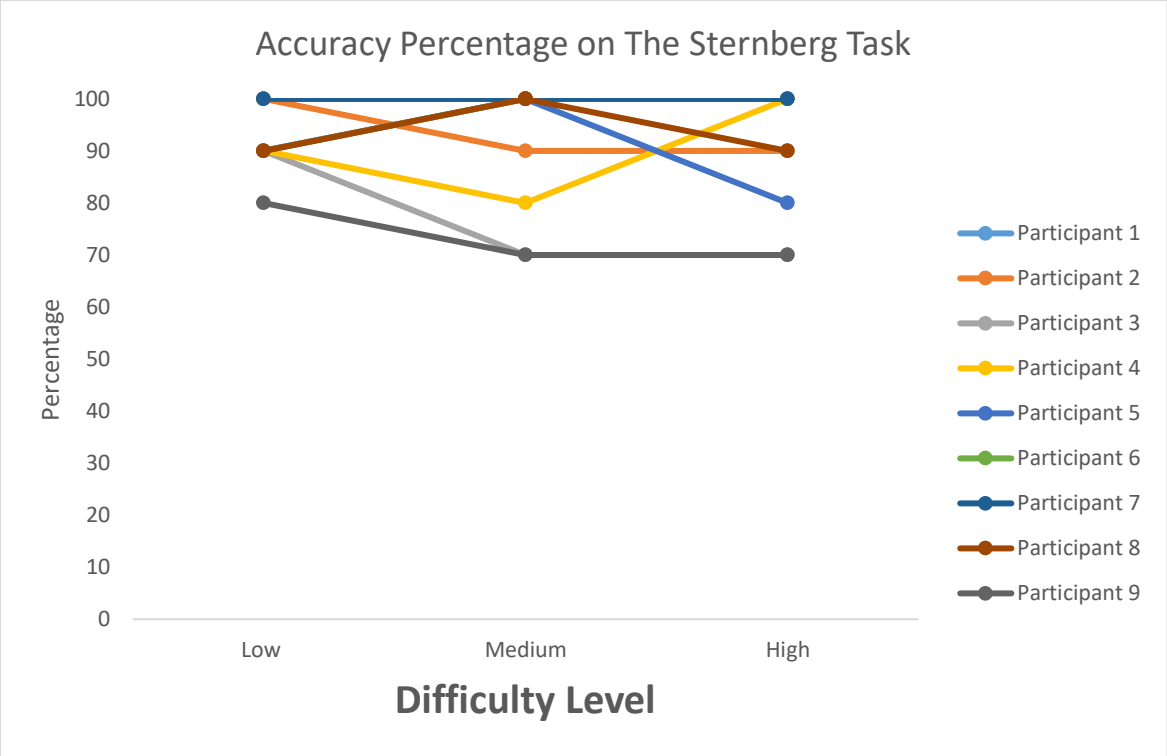
Table 6: Summary of demographic information and clinical characteristics of subject with chronic primary insomnia.

3.2. Cognitive Data

All nine participants completed the Sternberg task evaluating their working memory performance. Average percentage of correct answers (i.e. accuracy) were used as one of the two indicators of their working memory performance. The other indicator of the working memory capacity was the average reaction time of the participants. Only the trials in which the participants chose the correct answer were used to calculate the average reaction time. The Kruskal-Wallis test revealed that the increase in load of the Sternberg task did not impact accuracy ($H(2) = 0.1119$, $p = 0.9456$) and reaction time ($H(2) = 0.4127$, $p = 0.8135$) of patients with primary chronic insomnia. However, the average accuracy of participants' performance decrease with an increase in difficulty level. Three participants did not respond to at least one trial out of thirty.

Average Performance on the Sternberg Task		
Level of Difficulty	**Mean Accuracy (%) ± SD**	**Mean Reaction Time (seconds) ± SD**
Low Difficulty Level (5 Digits)	92.22 ± 6.67	1.57 ± 0.19
Medium Difficulty Level (6 Digits)	90.00 ± 13.23	1.62 ± 0.25
Highest difficulty Level (7 Digits)	88.89 ± 12.69	1.61 ± 0.31
Overall	90.37 ± 9.49	1.60 ± 0.23

Table 7: Quantification of working memory performance of our participants with insomnia in terms of mean accuracy and mean reaction time for each difficulty level and overall.



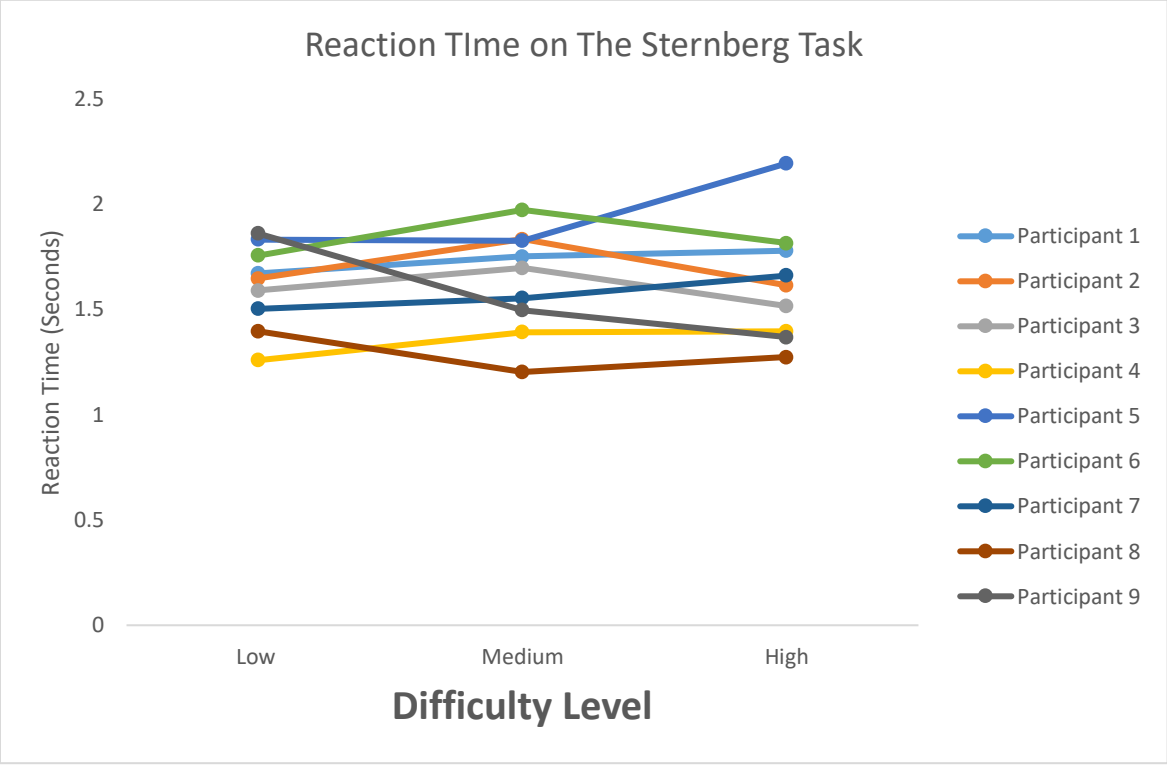


Figure 12: Accuracy percentage and reaction time of each participant in response to increase in difficulty level of the Sternberg task. Some participants had the same performance in terms of accuracy hence why some participants may not be visible in the first graph.

Lastly, the Spearman's correlation showed no link between insomnia severity and working memory performance of our participants with chronic insomnia (Accuracy: p = 0.72; RT: p = 0.72) . The same remained true when we explored the association of the BDI (Accuracy: p = 0.32; RT: p = 0.94), KSS (Accuracy: p = 0.40; RT: p = 0.77), subjective performance (Accuracy: p = 0.77; RT: p = 0.84), level of motivation (Accuracy: p = 0.99; RT: p = 0.91 and perception of task difficulty (Accuracy: p = 0.12; RT: p = 0.44) with working memory performance. Although none of the correlations were significant, the strength of correlation between majority of variables ranged from very weak to moderate. Only the relationship between perception of task difficulty and accuracy of performance on the Sternberg did not fall in this range. These two variables had an inverse relationship which deemed as strong (r=-0.7356).

	Performance	
	Accuracy	**Reaction Time**
ISI	p = 0.73 r = -0.14	p = 0.68 r = 0.17
BDI	p = 0. 33 r = 0.37	p = 0.94 r = 0.34
KSS	p = 0. 40 r = 0.31	p = 0. 78 r = -0.01
Subjective Performance	p = 0. 7778 r = 0.1449	p = 0. 8444 r = -0.1160
Motivation	p = 0. 9999 r = -0.0286	p = 0. 9194 r = -0.0857
Perception of Difficulty	p = 0. 1222 r = -0.7356	p = 0. 4444 r = -0.4119

Table 8. Correlation of the subjective measurements with working memory performance of our participants with insomnia.

3.3. MRI Data

3.3.1. Encoding Phase and Recall Phase Across All Difficulty Levels

Our results showed that left anterior cingulate gyrus, right cerebellum exterior cortex, bilateral inferior occipital gyrus and bilateral sub-gyral parietal lobe were activated during the encoding phase across all three levels of difficulty compared to the baseline. As for the recall phase, the cerebral activation pattern was composed of left middle frontal gyrus, left postcentral gyrus, left inferior parietal gyrus, right superior frontal gyrus, left postcentral gyrus, left inferior frontal gyrus, bilateral anterior insula, left sub-gyral parietal lobe (figure 15). In addition, several regions including left caudate tail, right caudate tail, left medial segment of superior frontal gyrus, left middle frontal gyrus, right posterior

cingulate gyrus and left angular gyrus were deactivated during the recall phase (figure 16). The exact coordinates of these regions can be found in tables 9, 10 and 17.

3.3.2. The Lowest Difficulty Level

During the encoding phase of the lowest difficulty level of the Sternberg task, we observed that the right occipital fusiform gyrus, left anterior cingulate gyrus, left inferior occipital gyrus, left lingual gyrus and left precuneus were more activated compared to the baseline (Figure 10). During the recall phase of the same level of difficulty, we observed a different pattern of activation. The regions that were activated during this phase were the right lingual gyrus, left central operculum, right inferior occipital gyrus, right inferior temporal gyrus, left precentral gyrus, left cerebellum exterior, right anterior insula, left thalamus, left inferior frontal gyrus and right anterior insula (Figure 10). We were unable to detect any deactivated regions during the encoding phase with our set criteria. This remained true for all levels of difficulty individually and combined. Hence, it is not reported in the subsequent paragraphs. As for the recall phase, we saw the right angular gyrus, right superior frontal gyrus, right caudate tail, left middle frontal gyrus and left posterior cingulate gyrus more deactivated compared to the baseline. See tables 11, 12 and 18 for this section.

3.3.3. The Medium Difficulty Level

Our analyses revealed two additional regions were activated during the encoding phase of the medium difficulty level of the Sternberg task compared to the previous difficulty level. These regions were the right inferior occipital gyrus and sub-gyral parietal lobule. However, a larger pattern of cerebral activation was observed during the recall phase. The activated regions that overlapped with the lowest difficulty level were the right inferior occipital gyrus, right anterior insula, left central operculum and left cerebellum exterior. Additional activated regions were the right superior frontal gyrus, left postcentral gyrus and left middle frontal gyrus. Small number of clusters were deactivated during the recall phase of this difficulty level. The peak of these clusters were the right medial frontal gyrus and right angular gyrus. See tables 13, 14 and 19 for this section.

3.3.4 The Highest Difficulty Level

Compared to the previous difficulty levels, additional activated cerebral regions in the encoding phase of the highest difficulty level were detected. These regions included the right cerebellum exterior (culman), left inferior frontal gyrus, right lingual gyrus, left inferior occipital gyrus, left superior parietal lobe and right medial frontal gyrus. The left anterior cingulate cortex was also activated which

overlapped with the two easier difficulty levels. Similar to the lowest and medium difficulty levels, we observed a larger pattern of cerebral activation during the recall phase. The additional activated brain regions during the recall phase compared to the two easier difficulty levels were the left fusiform gyrus, right inferior frontal gyrus, right cerebellar declive, right angular cortex and left superior parietal lobe. The right cerebellum exterior left middle frontal gyrus, right superior frontal gyrus, left inferior frontal gyrus, left postcentral gyrus, left central operculum, right inferior occipital lobe overlapped with activated regions in previous difficulty levels. As for the deactivated regions, we observed that the left middle frontal gyrus, left caudate tail, left precentral gyrus, left angular gyrus and right medial frontal gyrus were deactivated during the recall phase. See tables 15, 16 and 20 for this section.

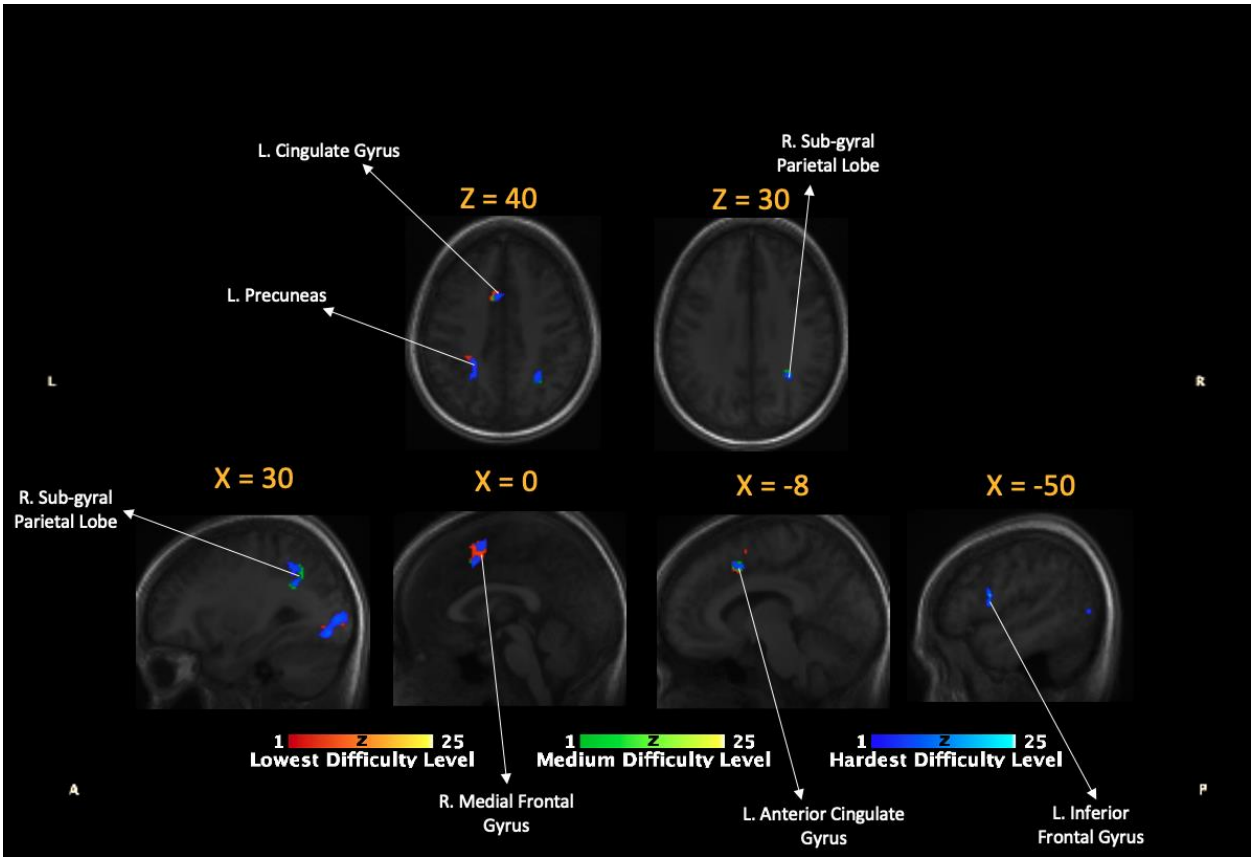


Figure 13: Activated brain regions in response to the encoding phase of the Sternberg task. Each colour is associated with a difficulty level as indicated in the figure.

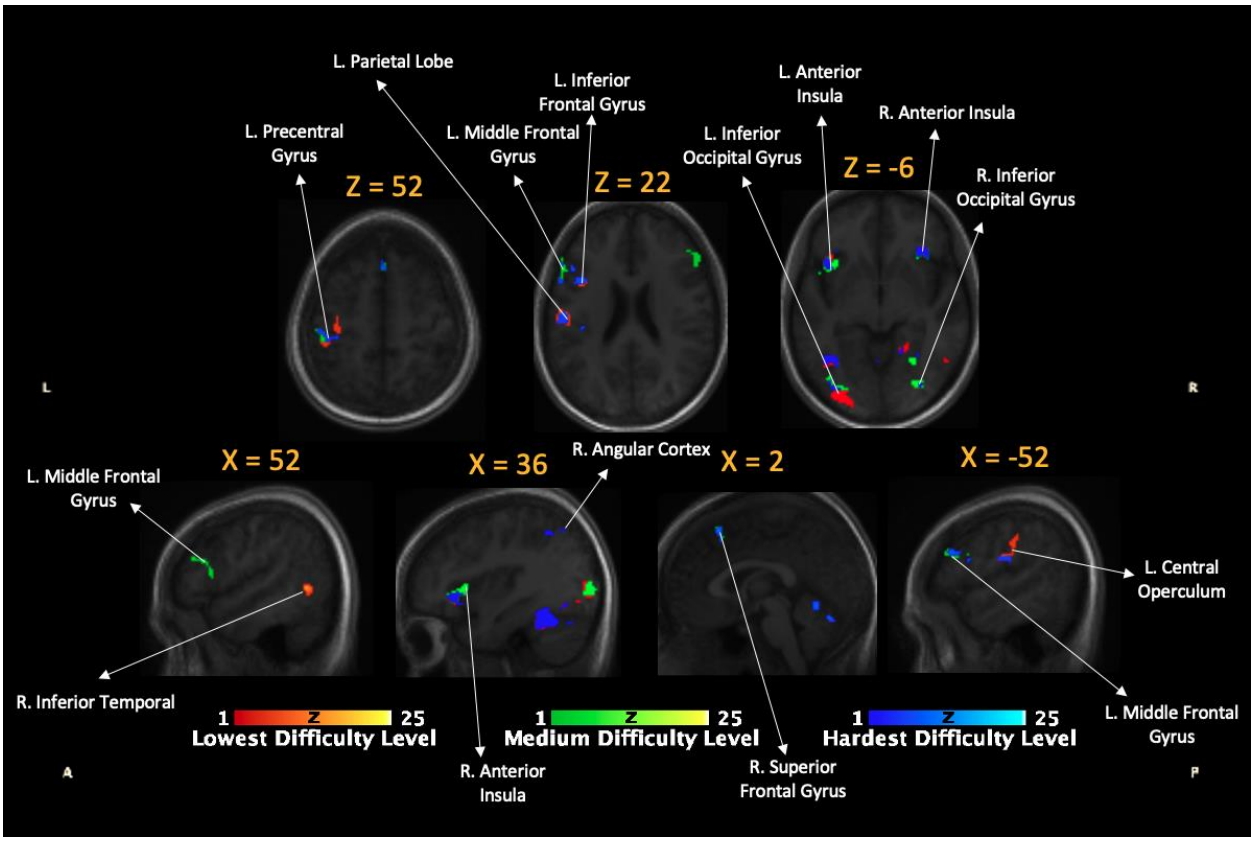


Figure 14: Activated brain regions in response to the recall phase of the Sternberg task. Each colour is associated with a difficulty level as indicated in the figure.

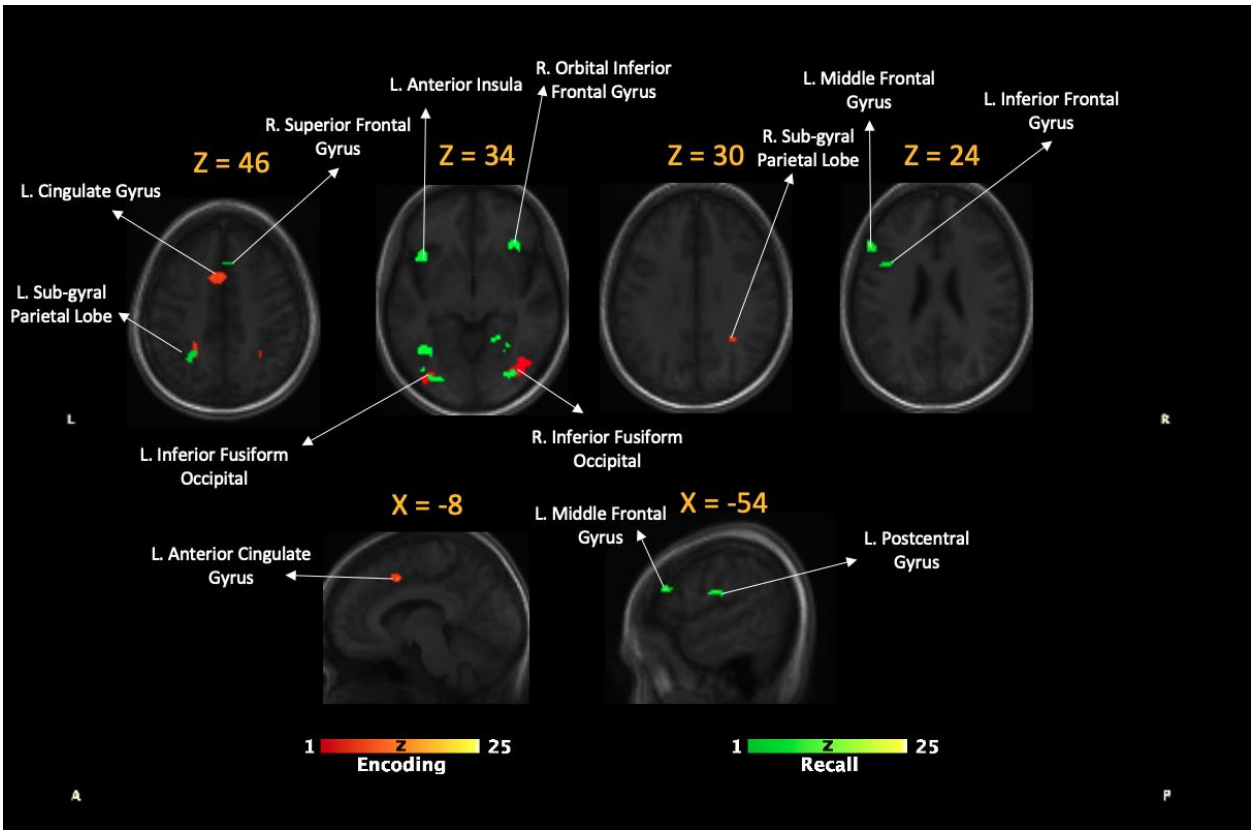


Figure 15: Activated brain regions in response to the encoding phase and the recall phase of the Sternberg task across all difficulty levels

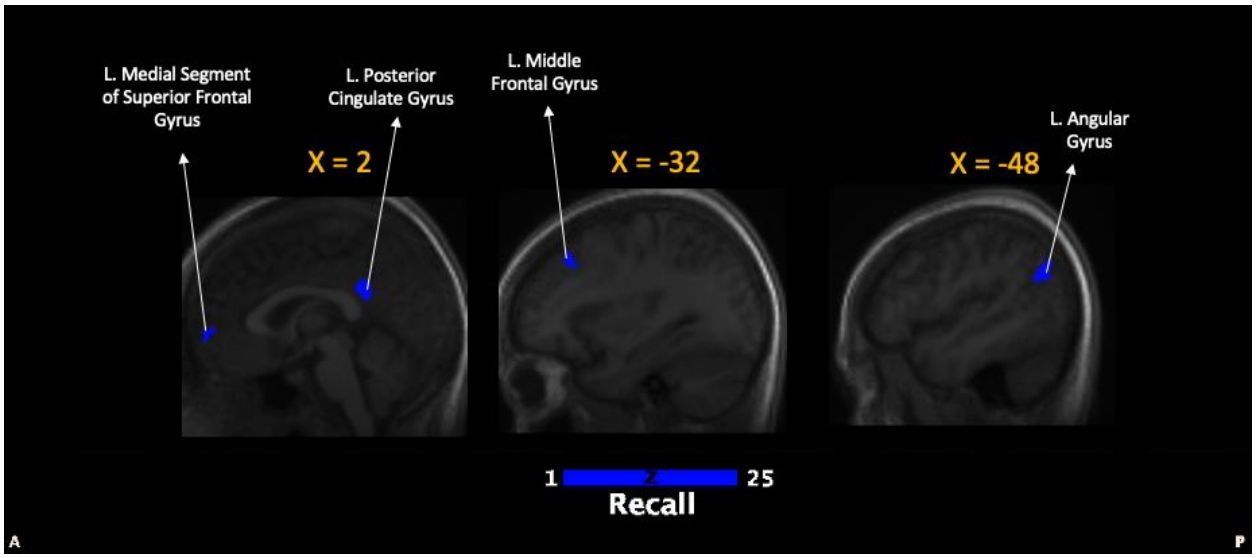


Figure 16: Deactivated brain regions in response to the recall phase of the Sternberg task across all levels of difficulty.

3.3.5. Effect of Task Load

We also examined the effect of the increase in load of the Sternberg task on cerebral activation pattern. The results demonstrated that when the difficulty level of the task increased, three clusters were significantly more activated during the encoding phase. The peaks of these clusters were in the right sub-gyral parietal lobe, left inferior occipital gyrus and left middle cingulate gyrus. In contrast to the encoding phase, no clusters larger than fifty voxels were activated in response to an increase in the task load during the recall phase. See table 21 for this section.

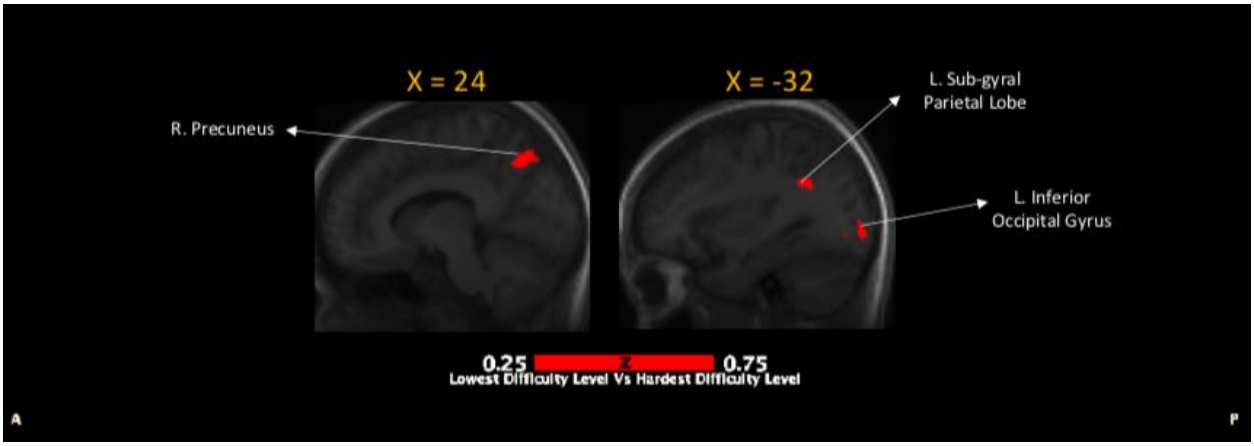


Figure 17: Activated brain regions in response to the increase in difficulty level during the encoding phase of the Sternberg task.

3.3.6. Regions of Interest

Using linear regression, we assessed the association of the working memory performance, subjective working memory performance and ISI with the cerebral activation in our regions of interest. Our analyses did not yield any significant results.

4. Discussion

Our study is the first neuroimaging investigation examining the working memory capacity of patients with chronic primary insomnia using the Sternberg task. We accomplished our goal of identifying activated brain regions in patients with insomnia in response to the Stenberg task. By using the Sternberg task, we were able to able to distinguish between activated cerebral regions for the encoding and recall phases of working memory. Previous findings of neuroimaging examinations in patients with insomnia did not make a distinction between activated brain regions for each working memory phase. This was due to the limitation of the task used in the past studies. In line with our primary hypothesis, we observed a different set of activated brain regions in insomnia for both phases of our task compared to previously reported activated regions during the Sternberg task in healthy participants. In contrast, our results failed to show that an increase in cognitive load of the Sternberg is associated with a decrease in working memory performance of patients with insomnia. However, a map of cerebral deactivation (As defined in the methods section) in response to the Sternberg task was detected for patients with chronic primary insomnia according to two working memory phases and three levels of difficulty. Lastly, linear regression analyses investigating the association of cerebral activation in response to the Sternberg task with subjective and objective working memory performance and ISI in patients with insomnia showed no significant results.

4.1. Working Memory Performance

As seen in the results section, the working memory performance of our participants was measured based on two parameters, the percentage of correct answers or accuracy and the reaction time to correct responses. Most of our participants had a near perfect accuracy percentage. Their reaction time was not negatively affected by an increase in cognitive load of the task. Nonetheless, we did see a decrease in performance in response to an increase in cognitive load. However, the decrease in performance was not statistically significant. This can stem from a few reasons. First, our sample size is small which makes it difficult to attain any significant results. The Sternberg task may have not been sensitive enough to detect subtle cognitive impairments. Another possibility could be that the increase in cognitive demand was not steep enough to impose any significant cognitive challenge. As it was previously suggested by a meta-analysis, many cognitive paradigms have been designed to detect

cognitive impairments in patients with major neurological or psychiatric disorders (E. Fortier-Brochu & Morin, 2014). Nevertheless, there have been studies that used different variations of the Sternberg task in healthy individuals and were successful to demonstrate a decrease in their cognitive performance in response to an increase in cognitive load (Altamura et al., 2007; Ashida et al., 2019; Cairo et al., 2004; Duncko et al., 2009; Sternberg, 1966). Two of these studies that used a letter version of the Sternberg task demonstrated that the accuracy of healthy participants dropped below 90% percent in trials with 8 stimuli, where they performance was significantly worse (Altamura et al., 2007; Cairo et al., 2004). In comparison, the average accuracy of each difficulty level fell below 90% for our highest difficulty level which contained 7 stimuli. This is comparable to previous studies. Also, the lack of significant decrease of accuracy in the highest difficulty level could raise the possibility that our version of the Sternberg could have been easy and more difficulty levels needed to see a decrease in working memory performance. On the other hand, we may have observed similar results as previous studies with a larger sample size.

Since the Sternberg task has not been previously used in this population, our working memory results cannot be directly compared to with the results of previous insomnia studies investigating working memory capacity. As mentioned in the introduction, previous studies comparing the objective working memory performance of patients with chronic insomnia and healthy participants reported inconsistent results. But, meta-analyses confirmed existence of objective working memory deficits in patients with chronic insomnia (E. Fortier-Brochu & Morin, 2014; Wardle-Pinkston et al., 2019).

4.1.1. Exploratory Analyses

Our results demonstrated that our subjective data, which included the ISI, BDI, KSS, subjective working memory performance, level of motivation and perception of task difficulty, are not associated with working memory performance. The ISI, a self-reported measure of insomnia severity symptoms, has been previously associated with worse episodic memory and sustained attention (Schmidt et al., 2010; Shekleton et al., 2014). Given how encoding and recall aspects of working memory rely on these two cognitive domains, we expected to see the same correlation between the ISI and working memory (Baddeley, 2000). But, previous working memory studies using different paradigms correlated the ISI with the working memory performance of the participants (Cellini et al., 2014; Drummond et al., 2013; Ling et al., 2020; Shekleton et al., 2010; Son et al., 2018). A potential reason for the lack of correlation in these studies was due to the absence of variation in insomnia severity according to the ISI, as this index was used to identify suitable participants for the study. In extension, it has been shown that shorter sleep duration is associated with worse cognitive performance (Khassawneh et al., 2018). Patients with insomnia do not always have a short sleep duration. Many of the studies mentioned above did not

consider the sleep duration of patients with insomnia the night before conducting a cognitive assessment. Another self-reported measure used in this study was the BDI that assesses depressive symptoms of the participants. Sleep problems are usually accompanied by a certain degree of depressive symptoms. Considering that depressive symptoms are associated with a worse working memory performance, we anticipated that we would see the same findings (Kizilbash et al., 2002; Salazar-Villanea et al., 2015) . However, this expectation was not reasonable as we excluded participants with depressive symptoms. Hence the BDI's range in our sample size was restricted to the lower end of the scale.

The KSS was not correlated with working memory of our participants. Previously, it had shown to be highly correlated with sustained attention performance in healthy individuals (Kaida et al., 2006). Given the importance of attentional processes in working memory, we intended to explore whether the KSS was also significantly correlated with working memory performance in patients with chronic insomnia. The KSS value among our participants indicated that they felt alert before the task with minor variations between participants. Two previous insomnia studies using the KSS did not correlate this variable with a specific cognitive domain (Losert et al., 2020; Perrier et al., 2014). Impairment of subjective performance of patients with chronic insomnia is a common observation in cognitive studies. Yet, the same studies were not always able to replicate subjective cognitive impairment of patients with insomnia using objective cognitive assessments (Ashida et al., 2019; Drummond et al., 2013; É. Fortier-Brochu et al., 2012; Shekleton et al., 2010; Wardle-Pinkston et al., 2019). In our study, we observed that the participants rated their working performance on the lower end of the scale. This is in line with previous insomnia investigations (Ashida et al., 2019; Drummond et al., 2013; É. Fortier-Brochu et al., 2012; Shekleton et al., 2010; Wardle-Pinkston et al., 2019). Given that the perception of stimuli or symptoms of patients with insomnia are not aligned with objective measurements, a lack of association between objective and subjective performance in our participants was not a surprise (Baglioni et al., 2014; Harvey & Tang, 2012; Huang et al., 2012). The average level of motivation of our patients with insomnia hovered around the middle of our scale with little variation. Their levels of motivation have not been associated with objective working memory performance in our study. An fMRI study investigating the brain activation of patients with insomnia during the N-back task found that the levels of motivation in this group of participants were lower compared to the control group after the MRI scan (Drummond et al., 2013). Our findings were not consistent with current evidence in individuals without sleep problems. Current evidence suggests that there is a positive correlation with motivation and working memory performance of young adults. The positive association remains true amongst older adults but to a lesser degree (Brose et al., 2010; Eccles & Wigfield, 2002). Hence, motivation may cause inter-individual variability in terms of working memory

performance. The lack of a positive association between motivation and working memory performance can be explained by little variation between working memory performance of participants.

4.2. Cerebral Activation in Response to The Sternberg Task

4.2.1. Neural Activation in Response to The Sternberg Task

According to our neuroimaging results, we observed different patterns of cerebral activation in the encoding phase compared to the recall phase. When we looked at the average neural response in the encoding phase for all three levels of difficulty, activated brain regions included the left cingulate gyrus, right cerebellum exterior, left inferior fusiform of occipital gyrus, bilateral lingual gyrus and bilateral sub-gyral parietal lobe. As for the recall phase, we observed activation in the bilateral cerebellum cortex, right anterior insula, left middle frontal gyrus, left postcentral gyrus, left inferior frontal gyrus, right superior frontal gyrus, left inferior frontal gyrus and left anterior insula. These findings are partially divergent with previous fMRI studies amongst healthy participants (Altamura et al., 2007; Ashida et al., 2019; Cairo et al., 2004). The encoding phase elicited activation of prefrontal gyrus and temporal lobe in healthy participants, but we did not observe the activation of these regions during this phase in our participants with insomnia. In addition, regions withing the temporal lobe were activated during the recall phase in healthy participants. The activation withing the temporal lobe was not replicated in this study.

The encoding phase and the recall phase were expected to yield different pattern of brain activation. This is supported by one of the established models of working memory that emphasizes the different phases of working memory function in synergy with different cognitive domains (Baddeley, 1992, 2000). This idea is also supported by alternative working memory models that have been theorized after Baddeley's working memory model (Kane & Engle, 2003; Oberauer, 2009). The encoding phase is believed to be attention driven and the recall phase is suspected to rely on episodic memory and executive function. Hence, this variation in cerebral response between phases of working memory is anticipated.

The BOLD response during the encoding phase, across three difficulty levels of the Sternberg task, indicated activation of the bi-lateral sub-gyral parietal lobes and left cingulate cortex in chronic insomnia. Lack of frontal cortex activation is interesting here as prefrontal regions have constantly been activated in the Sternberg task among healthy individuals (Altamura et al., 2007; Ashida et al., 2019; Cooper et al., 2012; Emch et al., 2019; Rottschy et al., 2012; Tomlinson et al., 2014). In addition, the frontoparietal network, also known as the central executive network, plays an essential role in working memory due to its association with attention control, initiation and of goal-oriented behaviours

regulation and online information maintenance (Habas et al., 2009; Marek & Dosenbach, 2018; Seeley et al., 2007). In fact, attention control suppresses the distracting stimuli for optimization of the encoding phase of working memory. Also, the encoding phase of the Sternberg task is a goal-oriented behaviour that, by extension, requires participants to temporarily store a set of new information (Baddeley, 2000; Sternberg, 1966). This is another reason why we are intrigued by the lack of prefrontal activation in the encoding phase in patients with chronic insomnia.

When observing the cerebral activation during the encoding phase for each difficulty level separately, we found that the right medial frontal gyrus was activated only at the highest difficulty level. This raises the question of whether the brain of patients with chronic insomnia are hypo-activated in response to a working memory task, or, the possibility that the lowest difficulty level of our Sternberg task was not cognitively demanding enough to significantly activate regions of the central executive network. We cannot describe our results as evidence of hypoactivation in patients with insomnia as we do not have a control group. This remains true for other presented hypotheses in this project. Also, researchers observed that patients with psychiatric or neurological disorders, such as depression, Alzheimer's disease, autism and schizophrenia experienced activation deficits in the prefrontal cortex regions and posterior parietal cortex in response to a working memory task (Menon, 2011). Interestingly, the risk of comorbidity of insomnia is increased among individuals with these disorders (Ju et al., 2014; Krystal, 2012; Shamim et al., 2019). It is beyond the scope of this project to discuss the directionality of the relation of insomnia and psychiatric and neurological disorders. On the other hand, the lack of significant activation in these regions can be attributed to our low number of participants.

Another brain region that was activated on average during the encoding phase was the bilateral sub-gyral parietal lobe. Also, the right sub-gyral parietal lobe was activated in our medium difficulty level and highest difficulty level. Other activated regions during the encoding phase, within the parietal regions, were left precuneus in the lowest difficulty level and left superior parietal lobe in the highest difficulty level. The relevance of parietal regions to working memory functioning is well recognized (Marek & Dosenbach, 2018). A coordinate-based meta-analyses demonstrated that intraparietal sulcus, superior parietal lobule and anterior parietal lobule were constantly activated across 189 working memory studies (Rottschy et al., 2012). A more recent study using the Sternberg task in healthy individuals showed that the superior parietal lobe was activated during the maintenance phase of the working memory (Ashida et al., 2019). This is similar to our findings of the highest difficulty level during the encoding phase in our participants. Although, we did not differentiate between the encoding and maintenance phase of working memory in our study. In addition to involvement of parietal regions

in the central executive network that control attention, the parietal regions have been shown to contribute to visual recognition by current evidence (Goodale & Milner, 1992; Pennick & Kana, 2012). Our study used a visual version of the Sternberg task. Therefore, the recognition and differentiation of the shape of the stimuli (i.e. digit) prior to their temporary storage in the visuospatial sketchpad was an important part of the encoding phase. As such, the activation of the parietal regions among patients with chronic insomnia seems to be appropriate. But it is impossible to determine whether these regions were hypo-activated or hyperactivated compared to healthy participants due to lack of a control cohort. This remains true for our future comparisons.

Moreover, one brain region that was activated in each of the three difficulty levels during the encoding phase was the dorsal anterior cingulate cortex. The dorsal anterior cingulate cortex is a part of the limbic system and pertains to the salience network. Its involvement in working memory has not been explored as extensively as the prefrontal cortex and the parietal regions (Emch et al., 2019; Menon, 2011). The regions within the cingulate cortex have constantly been activated in healthy individuals using a working memory paradigm (Ashida et al., 2019; Emch et al., 2019; Owen et al., 2005; Rottschy et al., 2012). The salience network has thought to be associated with identifying and selecting the most important external stimuli for internal processing (Dosenbach et al., 2006; Seeley et al., 2007). Therefore, it is expected for the brain regions that are a part of this network to be activated in response to goal-oriented tasks, like a working memory paradigm. As for patients with insomnia, only one study reported activation of the cingulate cortex, both anterior and posterior parts, during the N-back task (Drummond et al., 2013). As a matter of fact, they observed that the cingulate cortex is more activated during the task in patients with insomnia. The anterior cingulate cortex is a part of the salience network while the posterior cingulate cortex is a part of the DMN. The importance of this network in cognition was explained in the introduction. It has been hypothesized that the activation of the salience network is associated with inhibition of the DMN (Janes et al., 2016; Jilka et al., 2014; Menon, 2011; Northoff et al., 2007; Seeley et al., 2007). The synergistic relationship of these two networks has been shown to be important in many cognitive processes including working memory (Bush et al., 2000; Putcha et al., 2016; Washington & VanMeter, 2015). Hence, altered cerebral activation in these regions during a working memory task in patients with insomnia is an indicator that altered brain metabolism partially explain cognitive impairments in this population. Lastly, the lower deactivation of the DMN in response to a cognitive task has been associated with lower concentration of GABA, the main inhibitory neurotransmitter of the central nervous system, in the anterior cingulate cortex. Current evidence hypothesizes that lower global levels of GABA in patients with insomnia is a potential attributing factor to their physiological hyperarousal. This lends additional support to general physiological hyperarousal

theory introduced earlier in this paper, and its effect on cognitive functioning of patients with chronic insomnia

The most noticeable difference between activated regions in the encoding and the recall phase is within the frontal cortex, where we observed activation of the left middle frontal gyrus, left inferior frontal gyrus and right superior frontal gyrus. The activation of the parietal regions is slightly different compared to the encoding phase. In these regions, the activation is limited to the right superior parietal lobe and left postcentral gyrus. Based on these results, the frontoparietal activation during the recall phase is closer to what the past working memory experiments have shown in healthy participants (Altamura et al., 2007; Ashida et al., 2019; Cooper et al., 2012; Drummond et al., 2013; Emch et al., 2019; Rottschy et al., 2012; Sereno et al., 1995; Tomlinson et al., 2014). While there are hypotheses about the functional role of specific frontal regions, it is difficult to interpret every activated region within the prefrontal cortex as there is no general consensus on their functional organization (Eriksson et al., 2015; Marek & Dosenbach, 2018). But, it has been hypothesized that the right inferior frontal gyrus is specifically involved in attention control (Aron et al., 2003). In addition, parietal regions have been shown to contribute to retrieval of information in episodic memory and is essential in integration of information with prefrontal cortex (Cabeza, 2008; Marek & Dosenbach, 2018). Together, with the hypotheses that the recall phase of working memory relies on, episodic memory and integration of information from multiple sources is required for this phase. We believe this an appropriate pattern of activation in the recall phase.

Other activated regions, outside of the frontal and parietal regions, during the recall phase are the left anterior insula and right angular cortex. The anterior insula has been hypothesized to belong to the core working memory regions (Rottschy et al., 2012). The insula regions were also activated in response to the recall phase of the Sternberg task in healthy participants (Cairo et al., 2004). Therefore, it would be logical to expect that this region is associated with other cognitive processes that contribute to working memory. For instance, it has been shown that anterior insula is usually co-activated with the dorsolateral prefrontal and ventrolateral frontal areas during cognitive tasks (Menon, 2011). Additionally, literature suggests that the anterior insula contributes to attention processes and is involved in identifying the most relevant stimuli to guide behaviour (Lovero et al., 2009; Seeley et al., 2007). Nonetheless, the anterior insula has shown to be hyperactivated in individuals with anxiety. Since individuals with insomnia are at a higher risk of experiencing anxiety and that this region is a part of the arousal network, we believe the activation of anterior insula during working memory should be investigated more extensively in cognitive testing (Breslau et al., 1996; Weissman et al., 1997). It is not possible to confirm whether the activation of anterior insula and arousal network is higher in our

participants as suggested by the literature (Nofzinger et al., 2004), given the lack of control group. As for the angular cortex, the current evidence suggests this region plays a role in the episodic memory retrieval and integration of information, which are important aspects of the recall phase (Bréchet et al., 2018; Spaniol et al., 2009; Vatansever et al., 2017). Finally, the activated regions in the recall phase provide some evidence that necessary regions for appropriate working memory response are activated in patients with chronic insomnia.

Direct comparison of our results with previous fMRI studies investigating the working memory capacity among patients with chronic insomnia is challenging as the Sternberg task has never been used in such studies (Drummond et al., 2013; Li et al., 2016; Son et al., 2018) . As a result, the nuances of cerebral activation in the encoding phase versus the recall phase have never been explored in our population of interest. To make this more complicated, some of the previous experiments used different contrasts compared to our study. Yet, we observed similarities between our results and the results of these studies. For instance, Li et al. employed a spatial working memory paradigm to localize brain activity in patients with insomnia throughout the task. In their experiment, they observed activation in the right inferior frontal gyrus, bilateral superior parietal lobule and left angular cortex. However, the lateralization of these regions is different compared to our study. The most interesting one may be the left lateralized activation of inferior frontal gyrus in patients with insomnia during a spatial working memory task. A PET study hypothesized that a spatial and visual working memory task activates left side of the prefrontal cortex in younger adults, like the population used in Li. et al. (Reuter-Lorenz et al., 1999). In contrast, our study, that recruited a middle-aged participant with insomnia, observed a bilateral activation of the inferior frontal gyrus. Interestingly, the same PET study states that with an increase in age, it is more likely to observe a bilateral prefrontal cortex activation in response to a spatial and visual task (Reuter-Lorenz et al., 1999) .

4.2.2. Neural Response to Increase in Cognitive Load

Our study also examined the neural activation in response to an increase in cognitive load of the Sternberg task for the encoding and the recall phases separately. We only detected load-dependent regions during the recall phase. We found a significant increase in activation with increasing cognitive load in the following regions: the right precuneus, left sub-gyral parietal lobe and left occipital gyrus. The activation of the parietal regions in patients with chronic insomnia in response to an increase in load seems appropriate. This can be explained by the association of higher activation levels of frontoparietal regions with an increase in cognitive load of working memory tasks (Eriksson et al., 2015; Linden et al., 2003; Nyberg et al., 2009). This is plausible given the role of this region in maintenance of online information (Wendelken et al., 2008). More specifically, a coordinate-based

meta-analyses has shown, that a higher cognitive load leads to higher levels of activation of bilateral inferior frontal gyrus. It has been proposed that this activation is due to the involvement of caudal part of the lateral prefrontal cortex in memory capacity (D'Esposito et al., 2000; Owen et al., 1999; Rottschy et al., 2012).

4.2.3. Neural Deactivation in Response to The Sternberg Task

Our analyses demonstrated that a number of brain regions were deactivated in response to the recall phase of the Sternberg task in our participants. These regions are the bilateral caudate tail, left medial segment of superior frontal gyrus, left middle frontal gyrus, right posterior cingulate gyrus and left angular gyrus. Rahm et al. proposed that deactivation during a visual working memory is partially modulated by recognition (Rahm et al., 2014). This means it is possible that certain brain regions are deactivated in response to external stimuli to optimize their processing by the relevant regions. This hypothesis could partially explain why we observed deactivated regions in recall phase as our participants were required to recognize the presented stimuli in the MRI machine. In addition, the deactivated regions in our task are associated with the default mode network (Buckner & DiNicola, 2019; Vatansever et al., 2017). The deactivation of default mode-related regions during cognitive tasks, such as the working memory paradigm is not a new phenomenon and has been replicated before (Anticevic et al., 2012; Drummond et al., 2013; Marek & Dosenbach, 2018; Rahm et al., 2014). It has also been proposed that the deactivation of default mode network is due to inhibitory projections from task relevant regions to default mode network regions (Anticevic et al., 2012). Drummond et al. also saw similar patterns in patients with insomnia. They observed that there was higher level of deactivation of default mode network in healthy good sleepers compared to participants with chronic insomnia. They also observed that a worse subjective working memory performance was associated with lower deactivation of default mode network regions in patients with insomnia. Based on these results, they hypothesized that working memory deficits in patients with chronic insomnia can partially be explained by the lack of adequate deactivation of default mode network regions in patients with chronic insomnia. More recently, meta-regression analyses showed that higher levels of activation in left middle frontal gyrus, a default mode network region, is associated with longer reaction time in healthy individuals (Emch et al., 2019). This lends additional support to the hypothesis proposed by Drummond et al.

4.3. Strengths and Limitations

4.3.1. Strengths

In this study we utilized the Sternberg task that allowed us to distinguish between the pattern of cerebral activation in two phases of working memory in patients with chronic insomnia. Different cognitive processes are involved in different phases of working memory. Thus, we think that it is

important to make this distinction to fully understand the cognitive challenges that chronic insomnia may impose on patients by possible alteration of cerebral activation.

4.3.2. Limitations

The lack of a control group limits our interpretation of the results on our insomnia group, however, we have been able to compare the results to the literature. Another limitation was the presence of artifacts in our data. Inevitable head movements in the scanner introduce inaccuracies in functional localization of the brain (i.e. deactivation in the ventricles). There were also physiological causes that could introduce noise, such as changes in cardiac rhythm and breathing frequency as a result of performing a task. The first step to reduce the incident of such artifacts was motion correction during preprocessing. Lastly, we did not measure the sleep duration of the participants the night prior to performing our working memory task. Short sleep duration is a variable among patients with insomnia that can impact their cognitive performance on a task the following day. Furthermore, as previously mentioned, we acknowledge that our sample size was smaller compared to previous neuroimaging studies that examined the working memory capacity of patients with insomnia.

4.3.3. Future Studies

We discussed multiple relevant neural networks in our paper, however, we did not consider brain connectivity. We believe that localizing relevant cerebral regions is the first step towards understanding the neural correlates of the Sternberg task in patients with chronic insomnia. Our future studies will explore functional connectivity in this population. Additionally, functional localization may be an outdated approach to study the brain as different cognitive processes are associated with diffused cerebral activation patterns. Hence, approaches that combine different modalities of neuroimaging, such as magnetic resonance spectroscopy, with temporal dynamics analysis, like EEG, may be necessary to gain a more comprehensive appreciation of the neural basis of cognition in patients with chronic insomnia. Lastly, our larger longitudinal study has recorded data concerning other cognitive domains that can be used for future analyses to draw a clearer picture of cognitive impairment and possible cerebral activation alteration in patients with chronic insomnia.

4.4. Conclusion

The current study identified phase-dependant and load-dependent regions of cerebral activation and deactivation in patients with chronic primary insomnia during the Sternberg task. Many of the regions that were activated or deactivated were consistent with previous regions observed in both good sleepers and patients with chronic insomnia.

5. Appendix

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
L. Anterior Cingulate Gyrus	187	0.002	14.64	0.000	-8	8	44
L. Supplementary Motor Cortex			7.73	0.000	0	6	60
R. Cerebellum Exterior	79	0.030	12.75	0.000	42	-58	-24
L. Inferior Fusiform Occipital Gyrus	116	0.011	12.48	0.000	-36	-84	-10
L. Inferior Occipital Gyrus			6.71	0.001	-46	-78	0
R. Lingual Gyrus	392	0.000	11.20	0.000	22	-96	2
R. Inferior Occipital Gyrus			11.19	0.000	32	-88	4
R. Occipital Fusiform Gyrus			10.57	0.000	32	-76	-8
L. Lingual Gyrus	86	0.024	8.69	0.000	-22	-92	4
L. Occipital Pole			8.36	0.000	-14	-102	0
R. Sub-gyral Parietal Lobe	55	0.064	8.02	0.000	30	-52	30
R. Superior Parietal Lobe			7.71	0.000	26	-56	40
L. Sub-gyral Parietal Lobe	54	0.066	7.53	0.000	-24	-40	42
L. Superior Parietal Lobe			7.37	0.000	-22	-48	44

Table 9: Cerebral regions that were significantly activated in response to the encoding phase of the Sternberg task across all levels of difficulty. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Cerebellum Exterior	1191	0.000	28.40	0.000	16	-56	-16
R. Inferior Occipital Gyrus			27.74	0.000	32	-88	2
R. Fusiform Gyrus			20.36	0.000	24	-56	-12
R. Orbital Inferior Frontal Gyrus	132	0.000	26.50	0.000	34	26	-6
L. Cerebellum Exterior	858	0.000	17.66	0.000	-20	-70	-18
34L. Fusiform Gyrus			12.00	0.000	-28	-52	-18
L. Occipital Fusiform Gyrus			11.87	0.000	-26	-66	-14
L. Middle Frontal Gyrus	56	0.008	14.54	0.000	-56	26	24
L. Middle Frontal Gyrus			9.17	0.000	-52	32	28
L. Postcentral Gyrus	58	0.007	14.11	0.000	-56	-10	20
L. Inferior Frontal Gyrus	53	0.009	12.72	0.000	-38	12	20
R. Superior Frontal Gyrus	79	0.002	12.40	0.000	2	24	56
L. Supplementary Motor Cortex			7.10	0.000	-4	20	50
L. Medial Segment of Superior Frontal Gyrus			7.05	0.000	-2	26	40
L. Postcentral Gyrus	125	0.000	11.69	0.000	-40	-32	62
L. Postcentral Gyrus			6.25	0.001	-34	-30	52
L. Inferior Frontal Gyrus	136	0.000	11.23	0.000	-46	14	-10
L. Orbital Part of the Inferior Frontal Gyrus			9.96	0.000	-40	22	-8
L. Anterior Insula	54	0.009	8.63	0.000	-40	2	4
L. Sub-Gyral Parietal Lobe	64	0.005	7.03	0.000	-28	-54	44

Table 10: Cerebral regions that were significantly activated in response to the recall phase of the Sternberg task across all levels of difficulty. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

REGIONS (PEAK OF EACH CLUSTER IS INDICATED IN BOLD)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	P(uncorr.)	T	P(uncorr.)	X	Y	Z
R. Occipital Fusiform Gyrus	531	0.000	12.04	0.000	32	-78	-10
R. Inferior Occipital Gyrus			11.85	0.000	44	-82	2
R. Occipital Pole			11.79	0.000	22	-96	2
L. Anterior Cingulate Gyrus	257	0.000	11.88	0.000	-8	8	42
L. Supplementary Motor Cortex			10.56	0.000	-2	6	50
L. Supplementary Motor Cortex			10.02	0.000	0	6	60
L. Middle Occipital Gyrus	141	0.002	11.76	0.000	-36	-84	-8
L. Inferior Occipital Gyrus			7.38	0.000	-36	-90	2
L. Inferior Occipital Gyrus			6.98	0.000	-44	-82	-2
L. Inferior Occipital/Lingual Gyrus	124	0.003	10.32	0.000	-20	-90	2
L. Occipital Pole			10.17	0.000	-12	-102	2
L. Inferior Occipital Gyrus			8.60	0.000	-24	-98	2
L. Precuneus	54	0.038	9.19	0.000	-24	-44	44
L. Postcentral Gyrus			7.10	0.000	-26	-34	40
L. Superior Parietal Lobule			6.41	0.001	-24	-52	46

Table 11: Cerebral regions that were significantly activated in response to the encoding phase of the Sternberg task during the lowest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Lingual Gyrus	858	0.000	57.64	0.000	22	-54	-12
R. Cerebellum Exterior			41.96	0.000	40	-52	-28
R. Fusiform Gyrus			16.06	0.000	38	-44	-26
L. Central Operculum	165	0.000	38.61	0.000	-54	-16	22
L. Supramarginal Gyrus			8.41	0.000	-52	-26	34
R. Cerebellum Exterior			7.02	0.000	-50	-24	24
R. Inferior Occipital Gyrus	220	0.000	36.18	0.000	42	-86	-2
R. Middle Occipital Gyrus			30.09	0.000	30	-84	6
R. Inferior Occipital Gyrus	201	0.000	18.32	0.000	-26	-92	-4
R. Middle Occipital Gyrus			7.60	0.000	30	-84	-6
Lingual Gyrus			7.24	0.000	-20	-88	2
R. Inferior Temporal Gyrus	50	0.007	18.30	0.000	52	-58	0
L. Precentral Gyrus	150	0.000	17.05	0.000	-26	-24	66
Post Central Gyrus			10.47	0.000	-40	-32	60
Post Central Gyrus			8.46	0.000	-32	-32	62
L. Cerebellum Exterior	420	0.000	15.10	0.000	-18	-68	-20
Pyramis of Left Cerebellum			12.53	0.000	-2	-72	-24
Declive of Left Cerebellum			12.10	0.000	-32	-70	-12
R. Anterior Insula	63	0.003	15.06	0.000	34	28	-6
L. Thalamus	97	0.000	15.05	0.000	-18	-16	-2
L. Thalamus Proper			12.15	0.000	-22	-22	2
L. Thalamus Proper (Ven Lat Nucleus)			8.24	0.000	-14	-10	6
L. Inferior Frontal Gyrus	64	0.003	13.18	0.000	-40	10	20
L. Anterior Insula	60	0.004	8.69	0.000	-42	18	-6

Table 12: Cerebral regions that were significantly activated in response to the recall phase of the Sternberg task during the lowest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Inferior Occipital Gyrus	112	0.982	10.21	0.000	32	-92	6
R. Sub-Gyral Parietal Lobe	62	0.982	8.38	0.000	30	-50	30
R. Superior Parietal Lobule		0.982	7.79	0.000	26	-56	40
L. Anterior Cingulate Gyrus	56	0.982	7.96	0.000	-10	10	46

Table 13: Cerebral regions that were significantly activated in response to the encoding phase of the Sternberg task during the medium difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Inferior Occipital Gyrus	545	0.000	37.95	0.000	32	-88	4
R. Cerebellum Exterior			18.35	0.000	14	-60	-16
R. Inferior Occipital Gyrus			10.60	0.000	44	-84	0
R. Anterior Insula	280	0.000	21.65	0.000	36	24	-4
R. Middle Frontal Gyrus			13.81	0.000	50	20	16
R. Frontal Operculum			10.24	0.000	40	16	4
L. Central Operculum	301	0.000	14.18	0.000	-42	2	6
L. Anterior Insula			13.79	0.000	-40	20	-8
L. Anterior Insula			10.47	0.000	-36	14	-2
L. Cerebellum Exterior	640	0.000	13.38	0.000	-28	-54	-22
L. Occipital Fusiform Gyrus			11.18	0.000	-38	-72	-12
L. Occipital Fusiform Gyrus			10.04	0.000	-22	-72	-16
R. Superior Frontal Gyrus	71	0.004	10.82	0.000	2	24	56
L. Supplementary Motor Cortex			8.63	0.000	-6	20	50
L. Postcentral Gyrus	103	0.001	10.69	0.000	-40	-32	62
L. Postcentral Gyrus			6.37	0.001	-46	-26	48
L. Middle Frontal Gyrus	57	0.008	10.39	0.000	-52	30	28
L. Operculum Part of the Inferior Frontal Gyrus			6.51	0.001	-56	12	22

Table 14: Cerebral regions that were significantly activated in response to the recall phase of the Sternberg task during the medium difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Cerebellum Exterior (Culman)	117	0.004	24.97	0.000	40	-56	-24
L. Inferior Frontal Gyrus	74	0.017	20.71	0.000	-50	6	16
R. Lingual Gyrus	592	0.000	16.38	0.000	22	-96	2
R. Occipital Fusiform Gyrus			15.96	0.000	32	-78	-8
R. Inferior Occipital Gyrus			11.30	0.000	32	-88	2
L. Inferior Occipital Gyrus	379	0.000	16.36	0.000	-32	-82	-8
L. Inferior Occipital Gyrus			10.31	0.000	-20	-92	2
L. Supplementary Motor Cortex			8.15	0.000	-16	-102	0
L. Anterior Cingulate Gyrus	92	0.009	11.95	0.000	-8	8	44
R. Sub-Gyrus of Parietal Lobe	118	0.004	11.66	0.000	32	-52	30
R. Superior Parietal Lobule			9.18	0.000	26	-56	40
R. Superior Parietal Lobule			6.78	0.001	32	-48	48
L. Superior Parietal Lobe	88	0.010	7.65	0.000	-24	-52	46
L. Superior Parietal Lobule			7.63	0.000	-24	-40	40
R. Medial Frontal Gyrus	52	0.040	6.95	0.000	0	4	60

Table 15: Cerebral regions that were significantly activated in response to the encoding phase of the Sternberg task during the highest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at $p<0.001$ uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-level		Peak-level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
L. Fusiform Gyrus	1086	0.000	23.31	0.000	-28	-62	-16
L. Occipital Fusiform Gyrus			22.90	0.000	-22	-72	-16
L. Cerebellum Exterior			20.93	0.000	-38	-64	-30
R. Cerebellum Exterior	1101	0.000	20.73	0.000	18	-56	-18
Cerebral vermal lobules I-V			18.32	0.000	4	-60	-12
R. Cerebellum Exterior			14.49	0.000	38	-42	-28
L. Middle Frontal Gyrus	117	0.000	16.93	0.000	-52	22	26
L. Operculum Part of the Inferior Frontal Gyrus			10.39	0.000	-40	12	22
L. Operculum Part of the Inferior Frontal Gyrus			8.58	0.000	-56	12	20
R. Cerebellar Declive	92	0.001	15.12	0.000	10	-74	-20
L. Cerebellum Exterior			8.47	0.000	-2	-80	-24
L. Cerebellum Exterior			8.46	0.000	-6	-70	-20
R. Superior Frontal Gyrus	64	0.005	13.99	0.000	2	24	54
L. Supplementary Motor Cortex			8.22	0.000	-4	20	50
L. Medial Segment of Superior Frontal Gyrus			6.24	0.001	-6	26	44
L. Inferior Frontal Gyrus	102	0.001	12.94	0.000	-46	16	-10
L. Posterior Orbital Gyrus			9.07	0.000	-32	24	-10
L. Insula			8.24	0.000	-40	16	-2
L. Postcentral Gyrus	108	0.001	10.16	0.000	-38	-32	62
L. Postcentral Gyrus			8.17	0.000	-46	-24	54
L. Postcentral Gyrus			6.63	0.001	-34	-30	52
L. Central Operculum	131	0.000	10.15	0.000	-50	-12	18
L. Parietal Operculum			8.61	0.000	-38	-26	22
L. Posterior Insula			8.57	0.000	-32	-22	12
R. Inferior Occipital Lobe	52	0.010	9.23	0.000	32	-92	2
R. Inferior Occipital Gyrus			8.95	0.000	28	-84	4
R. Angular Cortex	64	0.005	9.10	0.000	36	-64	52
R. Superior Parietal Lobule			7.52	0.000	34	-52	48
R. Superior Parietal Lobule			6.30	0.001	28	-58	44
L. Superior Parietal Lobe	115	0.000	7.69	0.000	-28	-52	42

Table 16: Cerebral regions that were significantly activated in response to the recall phase of the Sternberg task during the highest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	p(uncorr.)	T	p(uncorr.)	X	Y	Z
L. Caudate Tail	76	0.003	21.80	0.000	-22	-42	18
L. Posterior Cingulate Gyrus			13.78	0.000	-22	-52	18
R. Caudate Tail	51	0.010	16.33	0.000	24	-42	14
L. Medial Segment of Superior Frontal Gyrus	76	0.003	11.78	0.000	-2	54	-2
R. Medial Segment of the Superior Frontal Gyrus			9.24	0.000	6	54	0
R. Medial Frontal Cortex			6.88	0.000	2	60	-8
R. Caudate Tail	111	0.000	10.80	0.000	58	-50	18
R. Angular Gyrus			10.22	0.000	52	-56	26
R. Angular Gyrus			9.02	0.000	48	-62	20
L. Middle Frontal Gyrus	74	0.003	9.95	0.000	-32	26	38
L. Middle Frontal Gyrus			8.40	0.000	-26	30	42
R. Posterior Cingulate Gyrus	99	0.001	8.42	0.000	2	-44	26
L. Angular Gyrus	88	0.001	8.22	0.000	-48	-62	26
L. Angular Gyrus			7.05	0.000	-50	-68	36
L. Angular Gyrus			6.67	0.001	-44	-72	28

Table 17: Cerebral regions that were significantly deactivated in response to the recall phase of the Sternberg task across all levels of difficulty. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	p(uncorr.)	T	p(uncorr.)	X	Y	Z
R. Angular Gyrus	187	0.000	24.41	0.000	48	-58	24
R. Angular Gyrus			17.29	0.000	58	-52	24
R. Angular Gyrus			9.69	0.000	52	-66	26
R. Superior Frontal Gyrus	62	0.003	18.73	0.000	20	44	42
R. Caudate tail	105	0.000	11.60	0.000	20	-34	22
R. Parahippocampus			9.88	0.000	14	-36	6
R. Lateral Ventricle			7.65	0.000	22	-42	16
L. Middle Frontal Gyrus	119	0.000	9.19	0.000	-28	30	46
L. Middle Frontal Gyrus			9.13	0.000	-22	28	38
L. Middle Frontal Gyrus			8.90	0.000	-34	32	40
L. Posterior Cingulate Gyrus	108	0.000	8.57	0.000	-10	-48	24
R. Posterior Cingulate Gyrus			7.31	0.000	2	-44	26
L. Posterior Cingulate Gyrus			6.78	0.001	0	-46	18

Table 18: Cerebral regions that were significantly deactivated in response to the recall phase of the Sternberg task during the lowest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	p(uncorr.)	T	p(uncorr.)	X	Y	Z
R. Medial Frontal Gyrus	145	0.000	16.89	0.000	14	56	0
L. Medial Segment of Superior Frontal Gyrus			11.92	0.000	-4	56	-2
L. Medial Frontal Gyrus			8.66	0.000	-16	54	8
R. Angular Gyrus	100	0.001	12.25	0.000	42	-60	24
R. Superior Temporal Gyrus			10.33	0.000	58	-54	18
R. Middle Temporal Gyrus			9.52	0.000	54	-58	26

Table 19: Cerebral regions that were significantly deactivated in response to the recall phase of the Sternberg task during the medium difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster size	p(uncorr.)	T	p(uncorr.)	X	Y	Z
L. Middle Frontal Gyrus	58	0.007	14.64	0.000	-26	28	40
L. Caudate Tail	55	0.008	14.33	0.000	-22	-40	18
L. Posterior Cingulate Gyrus			9.75	0.000	-20	-50	16
L. Precentral Gyrus	57	0.007	14.32	0.000	-6	-34	64
L. Angular Gyrus	107	0.001	11.09	0.000	-48	-68	32
L. Middle Temporal Gyrus			8.69	0.000	-44	-72	26
L. Middle Temporal Gyrus			7.47	0.000	-52	-72	24
R. Medial Frontal Gyrus	58	0.007	9.26	0.000	2	60	-4

Table 20: Cerebral regions that were significantly deactivated in response to the recall phase of the Sternberg task during the highest difficulty level. The Bold regions represent the peak of the cluster. (Thresholded at $p<0.001$ uncorrected)

Regions (Peak of Each Cluster is Indicated in Bold)	Cluster-Level		Peak-Level		Coordinates		
	Cluster Size	P(Uncorr.)	T	P(Uncorr.)	X	Y	Z
R. Precuneus	237	0.000	87.86	0.000	24	-64	38
R. Precuneus			10.85	0.000	10	-60	44
L. Inferior Occipital Gyrus			9.69	0.000	30	-78	26
L. Inferior Occipital Gyrus	236	0.000	18.03	0.000	-38	-86	4
L. Inferior Occipital Gyrus			14.37	0.000	-32	-90	-4
L. Inferior Occipital Gyrus			11.10	0.000	-36	-78	-4
L. Sub-gyral Parietal Lobe	54	0.004	14.95	0.000	-32	-52	30

Table 21: Cerebral regions that were significantly Activated in response to an increase in task difficulty during the encoding phase of the Sternberg. The Bold regions represent the peak of the cluster. (Thresholded at p<0.001 uncorrected)

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