SARA SİNEM SOZAN

EFFECT OF COVID-19 INFECTION

Bilkent University 2022

EFFECT OF COVID-19 INFECTION ON THE DEVELOPING BRAIN: PSYCHOSIS PRONENESS AND WORKING MEMORY ACTIVATION

A Master's Thesis

by
SARA SİNEM SOZAN

Department of
Psychology
İhsan Doğramacı Bilkent Univeristy
Ankara
August 2022

EFFECT OF COVID-19 INFECTION ON THE DEVELOPING BRAIN: PSYCHOSIS PRONENESS AND WORKING MEMORY ACTIVATION

The Graduate School of Economics and Social Sciences
Of
İhsan Doğramacı Bilkent University

by

SARA SİNEM SOZAN

In Partial Fulfillment of the Requirements for the Degree of
MASTER OF ARTS IN PSYCHOLOGY

THE DEPARTMENT OF
PSYCHOLOGY

İHSAN DOĞRAMACI BİLKENT UNIVERSİTY
ANKARA

August 2022

EFFECT OF COVID-19 INFECTION ON THE DEVELOPING BRAIN: PSYCHOSIS PRONENESS AND WORKING MEMORY ACTIVATION
By Sara Sinem Sozan

I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Timothea Toulopoulou
Supervisor

I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Ausaf Ahmed Farooqui
Examining Committee Member

I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Gözde İkizer
Examining Committee Member

Approval of the Graduate School of Economics and Social Sciences

---
Refet Gürkaynak
Director

DECLARATION

I work on Prof. Dr. Timothea Toulopoulou's program of research which focuses on understanding the cognitive, neurobiological, environmental, and genetic mechanisms that influence an individual's susceptibility to develop psychosis or build resilience. The protocol was already set up before I joined the Lab, and other students have been involved in the recruitment of controls and data collection. I have carved a slice of an ongoing research program that partly shifted focus to covid 19 since the pandemic started for my M.A. thesis, e.g., I am asking novel questions within an existing research framework. I have recruited and assessed all the covid patients myself.

ABSTRACT

EFFECT OF COVID-19 INFECTION ON THE DEVELOPING BRAIN: PSYCHOSIS PRONENESS AND WORKING MEMORY ACTIVATION

Sozan, Sara Sinem

M.A. in Psychology

Supervisor: Prof. Dr. Timothea Toulopoulou

Researchers have been investigating the effects of Covid-19 infection since late 2019. Symptoms caused by the SARS-Cov-2 virus varied from respiratory system failure to fatigue, brain fog and headaches. Studies showed that the infection leads to cognitive impairment and psychotic-like symptoms even after recovery. Literature has focused on hospitalized adult patients, and there is less information on how the developing brain exposed to the virus is affected. To address these gaps in the literature we investigated whether Covid-19 can be a risk factor for psychosis in adolescents and young adults. Forty individuals who were infected with Covid-19 and recovered at least two and at most four months before and 36 demographically matched controls were recruited in the study. Positive PCR test results confirmed the infection status of the participants. Subclinical psychosis was assessed using the Community Assessment of Psychic Experience (CAPE-42) questionnaire and the Structured Interview of Schizotypy - Revised (SIS-R) was used to assess psychotic-like symptoms. A functional magnetic resonance imaging was conducted during a well-known working memory task to investigate activation patterns. The working memory task involved seven tasks and a control motor task. Verbal fluency

performance was assessed in both phonetic and semantic categories. In order to control for the confounding effects of additional environmental risk factors for psychosis, paternal age, years of urban upbringing, cannabis exposure, and ethnicity were also considered. The findings revealed that although the two groups did not differ across different dimensions of the CAPE-42, the infected group had higher restricted affect and referential thoughts of being watched. Individuals infected with SARS-Cov-2 performed worse in both categories of the verbal fluency task. fMRI analysis revealed that individuals infected with the SARS-Cov-2 virus showed activation differences in the prefrontal cortex, medial temporal gyrus, middle frontal gyrus, and inferior parietal gyrus. Higher performance in the verbal fluency task predicted greater activation during the working memory task. These results suggest that exposure to the Covid-19 infection during brain development can be an environmental risk factor for psychosis.

Keywords: Covid-19 infection, psychosis risk, psychosis proneness, functional magnetic resonance imaging, working memory

ÖZET

COVID-19 ENFEKSIYONUNUN GELİŞMEKTE OLAN BEYİN ÜZERİNDEKİ ETKİSİ: PSİKOZ YATKINLIĞI VE ÇALIŞMA BELLEĞİ AKTİVASYONU

Sozan, Sara Sinem

Yüksek Lisans, Psikoloji

Tez Danışmanı: Prof. Dr. Timothea Toulopoulou

2019'un sonlarından bu yana Covid-19 enfeksiyonunun etkileri araştırılmaktadır. SARS-Cov-2 virüsünün neden olduğu semptomlar, solunum sistemi yetmezliğinden, yorgunluk, beyin sisi ve baş ağrılarına kadar çeşitlilik göstermektedir. Çalışmalar, enfeksiyonun aynı zamanda, iyileşmenin ardından dahi bilişsel bozukluklara ve psikoz benzeri semptomlara yol açtığını göstermektedir. Literatürdeki çalışmalar çoğunlukla hastane yatışı olan yetişkin hastalara odaklanmıştır ve virüse maruz kalan genç bireylerde, gelişmekte olan beynin nasıl etkilendiği konusunda az bilgi bulunmaktadır. Bu çalışmada, literatürdeki bu eksiklikleri ele almak için Covid-19'un ergenlerde ve genç yetişkinlerde psikoz için bir risk faktörü olup olmadığı araştırılmıştır. Çalışmaya Covid-19 enfeksiyonu geçirip en az iki en fazla dört ay önce iyileşmiş olan 40 birey ve demografik olarak eşleştirilmiş 36 kontrol katılımcısı dahil edilmiştir. Katılımcıların enfeksiyon durumu pozitif PCR test sonucu ile doğrulanmıştır. Subklinik psikoz, Toplumda Psişik Yaşantıları Değerlendirme Ölçeği (CAPE-42) kullanılarak değerlendirilmiştir. Psikoz benzeri semptomların değerlendirilmesi için Şizotipi için Yapılandırılmış Görüşme- Gözden Geçirilmiş Form (SIS-R) kullanılmıştır. Beyin aktivasyonu farklılıklarını araştırmak için iyi bilinen bir çalışma belleği testi sırasında fonksiyonel manyetik rezonans görüntüleme tekniği

kullanılmıştır. Çalışma belleği testi 7 adet görev ve bir kontrol motor görevi içermektedir. Sözel akıcılık performansı hem fonetik hem de semantik kategorilerde değerlendirilmiştir. Psikoz için çevresel risk faktörlerinin etkilerini kontrol etmek için baba yaşı, kent yaşantısı, esrar kullanımı ve etnik köken gibi faktörler de dikkate alınmıştır. Bulgular, iki grubun CAPE-42'nin farklı boyutlarında farklılık göstermemesine rağmen, enfeksiyon geçiren grubun daha yüksek sınırlı duygulanım ve izlenme düşüncelerine sahip olduğunu ortaya koymuştur. SARS-Cov-2 virüsüne maruz kalan kişiler, sözel akıcılık testinin hem fonetik hem de semantik kategorilerinde daha düşük performans göstermiştir. Fonksiyonel manyetik rezonans analizi, enfekte olan kişilerde prefrontal korteks, medial temporal girus, medial frontal girus ve inferior parietal girusta aktivasyon farklılıkları gösterdiğini ortaya koymuştur. Sözel akıcılık testinde daha yüksek performans, çalışma belleği testi sırasında daha yüksek aktivasyon ile korelasyon göstermiştir. Bu sonuçlar, Covid-19 enfeksiyonuna maruz kalmanın psikoz için bir çevresel risk faktörü olabileceğini düşündürmektedir.

Anahtar kelimeler: Covid-19 enfeksiyonu, psikoz riski, psikoz yatkınlığı, fonksiyonel manyetik rezonans görüntüleme, çalışma belleği

ACKNOWLEDGEMENT

Firstly, I would like to thank **Prof. Dr. Timothea Toulopoulou** for giving me the opportunity to be a part of her research team and allowing me to work on this topic of research. She has been a great advisor along the way with her support and feedback.

I am deeply grateful to have worked with **Dr. Helin Yılmaz Kafalı and Dr. Müge Mutlu**. They have been a sincere source of support for all the steps I took to complete this thesis.

With all my heart, I want to praise **Bülent Ark Akan** for being the greatest source of love and positivity both in my life and during the process of my graduate education. This thesis would not be possible without him.

I also would like to thank my father **Volkan Sozan**, my mother **Selma Ahi** and my brother **Ahmet Cemil Sozan** for encouraging me to pursue my academic career and being supportive along the way.

I am thankful to my colleagues in the **Brain Development and Psychosis Lab** for being great co-workers and friends. They helped me with all the questions and hesitations I had along the way.

TABLE OF CONTENTS

ABSTRACT..... iii

ÖZET..... v

LIST OF TABLES..... ix

LIST OF FIGURES..... x

CHAPTER 1: INTRODUCTION..... 1

1.1 A Brief Overview of Covid-19 Infection..... 1

1.2 A Brief Overview on Brain Development and Psychosis Proneness……2

1.2.1 Psychosis and Working Memory…….…….. 2

1.2.2 Regions Associated with Working Memory Deficits Related to Psychosis…… 4

1.2.3 Verbal Fluency and Psychosis Proneness……. 6

1.3 Infection as an Environmental Risk Factor for Psychosis…….. 7

1.4 The Relationship Between Covid-19 and Psychosis…….. 8

1.5 The Relationship Between Covid-19 infection and Executive Function…….9

CHAPTER 2: METHODS……...……... 11

2.1 Participants..... 11

2.2 Behavioral Data..... 12

2.2.1 Assessment of Psychosis Proneness..... 12

2.2.2 Assessment of Psychosis Risk..... 12

2.2.3 Assessment of Verbal Fluency..... 13

2.3 Cognitive Paradigm (Working Memory Paradigm) 13

2.4 MRI Scanner..... 15

2.5 Acquisition of Functional Images..... 16

2.6 Analysis of Functional Images..... 16

2.6.1 Preprocessing..... 16

2.6.2 Statistical Analysis..... 17

CHAPTER 3: RESULTS..... 19

3.1 Analysis of Demographic Data..... 19

3.2 Analysis of Behavioral Data..... 19

3.3 Task-Based Activation Results..... 26

CHAPTER 4: CONCLUSION AND DISCUSSION..... 34

REFERENCES..... 39

APPENDIX..... 46

LIST OF TABLES

2.3.1 Cognitive subtractions used for each contrast..... 17

3.1.1 Demographics and environmental risk factors..... 21

3.2.1 Descriptive statistics and results for behavioral data…… 22

3.2.2 Descriptive Statistics and results for SIS-R scores..... 23

3.3: Peak coordinates and results for Working Memory Task..... 33

LIST OF FIGURES

1.2.2.1 Demonstration of the multicomponent model for regions associated with working memory..... 6

2.3.1 Demonstration of tasks within the cognitive paradigm..... 15

3.2.1 Comparative bar chart of SIS-R Restricted Affect Scores..... 24

3.2.2 Comparative bar chart of SIS-R Referential thoughts of being watched..... 24

3.2.3 Comparative plot of phonetic verbal fluency scores 25

3.2.4 Comparative plot of semantic verbal fluency scores 25

3.3.1 Activation differences in the middle temporal gyrus associated with estimation without working memory..... 29

3.3.2 Activation differences in the middle frontal gyrus associated with computation and estimation without working memory..... 29

3.3.3 Activation differences in the left middle frontal gyrus associated with computation and estimation after encoding..... 30

3.3.4 Activation differences in the inferior parietal lobule associated with manipulation of information in working memory..... 30

3.3.5 Activation differences in the middle frontal gyrus associated with computation during encoding..... 31

3.3.6 Activation differences in the inferior parietal lobule associated with numerical size judgement outside working memory.....31

3.3.7 Activation differences in the medial frontal gyrus associated with encoding 32

CHAPTER 1

INTRODUCTION

1.1 A Brief Overview on Covid-19 Infection

In late 2019, cases of pneumonia-like symptoms caused by a novel coronavirus (2019-nCov, later called SARS-Cov-2) were reported in Wuhan, China, then spread around the world quickly (Huang et al.,2020). Around thirty thousand people were infected in less than two months, and hundreds of mortal cases were reported (Wu, Chen & Chan, 2020). This rapid spread of the infection is believed to have been caused by a lack of knowledge about disease transmissibility and protection. Later it was discovered that although the origin of the infection is zoonotic or animal-based, several reported cases have confirmed that person-to-person contact is a serious agent for the spread of the infection (Wu et al., 2020). The reported symptoms have varied from severe respiratory system failure to mild headaches, brain fog, and fatigue.

Several scientific studies have been conducted to investigate the effects of the SARS-Cov-2. There is strong evidence that Covid-19 infection is related to virus-induced neuroinflammation, leading to anatomical and functional changes in the brain (Douaud et al., 2022). This thesis aims to investigate whether these changes in the brain can be a risk factor for psychosis and schizophrenia.

1.2 A Brief Overview on Brain Development and Psychosis Proneness

1.2.1 Psychosis and Working Memory

Psychosis is an altered state of the mind defined by symptoms such as delusions and hallucinations. The American Psychiatric Association and The World Health Organization define psychosis with an emphasis on the lack of insight into the pathological nature of these symptoms (Arciniegas, 2015). Psychotic symptoms are seen in several medical conditions, such as schizophrenia, schizoaffective disorder, and other psychotic mental disorders such as brief psychotic disorder. A subset of the population tends to develop psychotic symptoms due to genetic, developmental, or environmental risk factors (Arciniegas, 2015).

Certain environmental factors such as being raised in an urban area, use of cannabis, exposure to childhood trauma, prenatal and birth complications, late paternal age and migration contribute to the risk for psychosis (Dean & Murray, 2022). For instance, studies have shown that not only first-generation immigrants, but also second-generation immigrants are at high risk for schizophrenia and other psychotic disorders (Bourque, van der Van & Malla, 2011). Being raised in an urban area is associated with increased risk for later development of psychosis (Fett, Lemmers-Jansen & Krabbendam, 2019). Several explanations have linked urban upbringing to increased risk for exposure to infection, cannabis use, discrimination, and social fragmentation (Stilo & Murray, 2019). Exposure to abuse, neglect or trauma during childhood is associated to increased risk for psychosis in adulthood, especially positive symptomatology including hallucinations (Bentall et al., 2014). The interaction between these environmental and developmental

risk factors and genetic susceptibility is the most recent model for the emergence of psychotic disorders (Toulopoulou et al., 2019).

Studies have shown that symptoms such as ideas of reference, unusual thought content, impairment in maintaining attention, disturbances in processing information, disorganized speech and perceptual impairment are significantly associated with increased risk for later transition to psychosis (Demjaha et al., 2012).

Cognitive impairments often accompany psychotic disorders. Researchers have indicated that cognitive impairment is not secondary to psychotic symptoms. The genetically heritable nature of psychosis has led several scales to be developed to assess the vulnerability in nonpatients. Individuals who scored higher on these scales show similar psychological and neurocognitive impairments to those experienced by schizophrenia patients (Horan, Reise, Subotnik, Ventura & Nuechterlein, 2008) (Reichenberg, 2005).

Cognitive deficits are one of the key features of psychosis, working memory deficit being particularly critical. Previous studies with psychosis patients and their unaffected relatives have shown that deficits in working memory can indicate psychosis risk (Zhang, Picchioni, Allen, & Toulopoulou, 2016; Pukrop et al., 2007). Interestingly, healthy individuals with subclinical symptoms of psychosis (often referred to as psychosis-proneness or schizotypy) show less prefrontal cortex activation and worse performance in working memory. This finding suggests that individuals at risk of psychosis show early signs in the absence of diagnosis. Indeed, Pukrop and colleagues

(2007) have shown that among individuals at risk for psychosis, those who later develop psychosis show less brain activation and lower working memory performance when compared to those who did not convert to psychosis.

Working memory is defined as a set of cognitive processes that include the encoding, manipulation, and retrieval of information. This complex process requires several cortical and subcortical regions, such as the prefrontal, parietal, and basal ganglia (Trutti, Verschooren, Forstmann, & Boag, 2021). From late childhood to early adulthood, selective activation of the brain regions related to a given task increases, pointing to the peak maturation of the cortex (Casey, Tottenham, Liston, & Durston, 2005). Several studies investigated the regions activated during different working memory stages in adult and adolescent brains.

1.2.2 Regions Associated to Working Memory Deficits Related to Psychosis

Working memory is prominently associated with activation in the frontal and parietal regions of the brain. Studies have shown that prefrontal cortex (PFC) and parietal regions are highly correlated with working memory processing (Zhang et al., 2016; Tan et al., 2012). Previous literature has shown that dorsolateral prefrontal cortex (DLPFC) is associated with integration, maintenance, and manipulation of information within working memory while the connections between the DLFPC and subcortical regions such as right and left caudate are associated with encoding information into working memory (Chai, Abd Hamid & Abdullah, 2018). Another critical region in the higher levels of working memory processing is the superior frontal gyrus (SFG). Studies have

shown that legions in the left SFG is associated to working memory impairments (Boisgueheneuc et al., 2006).

Metanalyses have shown reduced activation in the right middle frontal and right inferior frontal gyri seen in first-degree relatives of people diagnosed with schizophrenia compared to healthy controls. Another significant finding is that while schizophrenia patients tend to perform worse in working memory tasks, better performance (lower number of errors and missed answers) is associated with increased activation in the DLPFC within the patient group (Manoach et al., 2000). Studies have shown that relatives of psychosis patients showed increased activation in the left inferior parietal region compared to healthy controls pointing to the heritability of psychosis being expressed via changes in cortical activation (Zhang et al., 2016).

Another region that is shown to be associated with working memory through neuroimaging studies is the basal ganglia. According to the neurocomputational model, basal ganglia are a gateway in the working memory process via circuits between the prefrontal cortex and thalamus (Trutti et al.,2021). Neurocognitive studies have shown that higher performance in a working memory task is associated with higher activity in the prefrontal cortex and basal ganglia. An fMRI study by Yoon and colleagues (2013) revealed that schizophrenia patients showed decreased activation in the basal ganglia, specifically in left and right head of the caudate, and lower performance during a working memory task when compared to healthy controls. During the encoding phase of working memory, schizophrenia patients showed lower activation in the ventral striatum, a subregion of the basal ganglia (Huang et al., 2019).

1.2.3 Verbal Fluency and Psychosis Proneness

Verbal fluency is another significantly impaired cognitive function in psychosis (Meijer et al., 2011). It is typically assessed by asking individuals to retrieve words that belong to a particular category and avoid repetition, thus utilizing executive function (Shao, Jense, Visser & Meyer, 2014). Studies have shown that in individuals with a high clinical risk for psychosis, negative symptoms are negatively associated with cognitive impairment, specifically verbal fluency performance. (Leanza et al, 2018), indicating that as the negative symptoms get severe, individuals perform worse in a verbal fluency task.

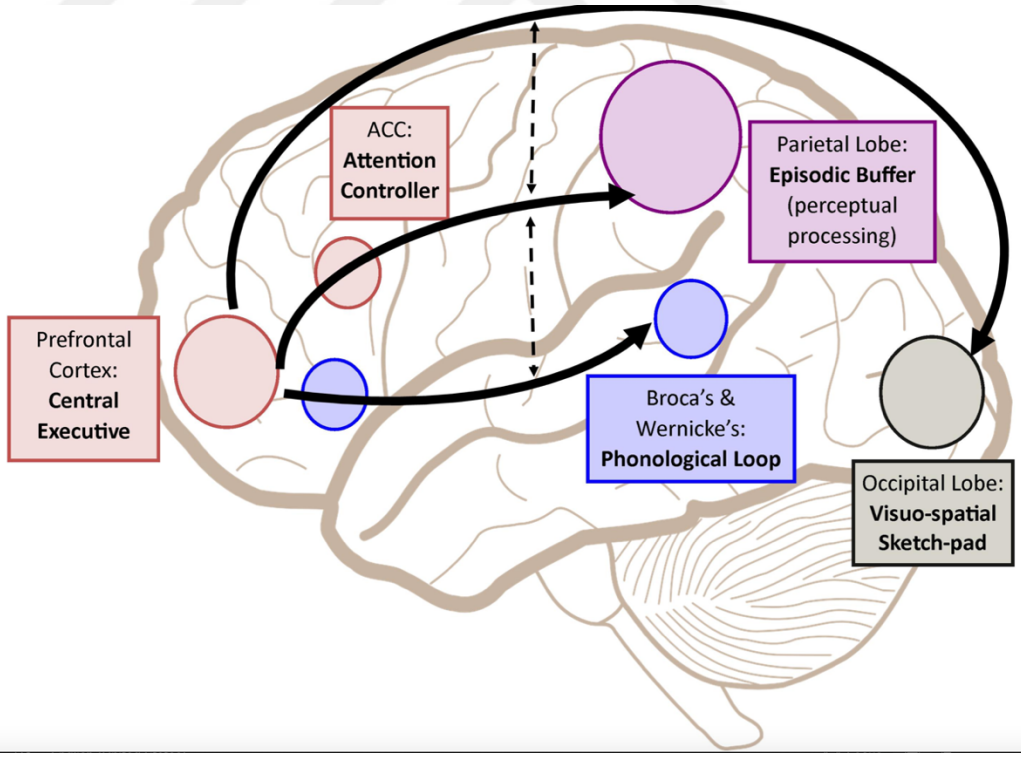


Figure 1.2.2.1: Although working memory is a complex process that engages multiple regions of the brain, a simplified depiction of the multicomponent model for the regions associated to working memory (Bradley, 2010, as cited in Chai, Abd Hamid & Abdullah, 2018)

Meijer and colleagues (2011) have shown that lower semantic verbal fluency scores significantly correlated with lower density in the gray matter volume in individuals at high clinical risk for psychosis. Functional changes in the brain are also associated with verbal fluency scores. For example, Holper and colleagues (2015) have shown that during a verbal fluency task, individuals with higher subthreshold psychotic symptoms, namely psychotic experiences that are clinically less severe or not relevant, show decreased activation in prefrontal and temporal cortices. Becker and colleagues (2009) found that verbal fluency performance in first episode psychosis patients and individuals who are at high risk for schizophrenia did not differ significantly but both groups performed worse compared to the healthy controls.

1.3 Infection as an Environmental Risk Factor for Psychosis

Infection has been hypothesized as a potential risk factor for the pathogenesis of psychosis. Certain infectious agents such as toxoplasma and hepatitis C have been studied regarding the relationship between infection and neuropathology (Benros & Mortensen, 2019; Hartwig, Borges, Horta, Bowden, & Smith, 2017). Previous literature shows that an infection that could affect the central nervous system could increase the risk for psychosis by affecting protein synthesis (Kepinska et al.,2020).

Comer and colleagues (2020) have stated that postmortem investigation of medial prefrontal cortex tissues of individuals with schizophrenia show changes in the gene expression responsible for the blood-brain barrier permeability. As the blood-brain barrier permeability increases, brain tissues could become vulnerable for infection that

could lead to psychosis. Retrospective studies have revealed a significant interaction between admission to hospital due to infection during childhood and increased risk for schizophrenia later (Debost et al., 2020), but this relationship's direction needs further investigation.

1.4 The Relationship Between Covid-19 Infection and Psychosis

Previous epidemics of respiratory system infections were associated with psychiatric disorders, including psychosis (Iqbal et al., 2020; Rogers et al., 2020; Troyer, Kohn & Hong, 2020). Recent studies show that COVID-19 is also associated with an increased risk for psychiatric disorders, particularly post-traumatic stress disorder and depression (Torales, O'Higgins, Castaldelli-Maia, & Ventriglio, 2020).

Several studies and case reports have been published reporting individuals experiencing brief periods of psychotic symptoms following infection with Covid-19 (Zulkifli, Sivapatham, & Guan, 2020; Ferrando et al., 2020; Hellmuth et al., 2020; Parra et al., 2020). Although it is still unclear whether the environmental stress created by the pandemic, admission of higher doses of steroids during treatment (Brown et al., 2020), or the infection with the virus itself is the main cause of these psychotic symptoms, research has shown that infection with SARS-Cov-2 virus is significantly associated with psychosis.

Aside from the viral infection itself, the SARS-Cov-2 pandemic had social, economic, and psychological effects on individuals. In a study conducted by Kira and colleagues (2021), researchers found that traumatic stress related to Covid-19 had significant and

direct effects on working memory and inhibition among Syrian refugees in Turkey. The effect of Covid-19 on executive function is found to be independent of hospitalization.

1.5 The Relationship Between Covid-19 infection and Cognitive Impairment

With the novelty and broad scope of the symptoms, COVID-19 infection has been the interest of several researchers since the pandemic. Several brain imaging studies were conducted on the effects of the infection on the brain. Postmortem studies have found structural abnormalities, including signal abnormalities and hemorrhagic lesions, in individuals who died from the infection (Coolen et al., 2020; Kremer et el., 2020). An important finding by Fischer and colleagues (2020) is that structural MRI scans revealed hyperintensiticity and diffusion restriction of the basal ganglia, which is a region that is significantly associated with working memory. Hypermetabolism in the frontoparietal regions in the brain is also linked to cognitive decline and executive function deficits, such as in working memory and verbal fluency, in individuals infected with the SARS-Cov-2 virus (Hosp et al., 2021).

Hosp and colleagues (2021) have indicated that 18 of 26 patients infected with SARS-Cov-2 showed cognitive impairment using an extended neuropsychological battery. Hellmuth and colleagues (2021) observed executive function deficits in young and middle-aged individuals who were not hospitalized after being tested positive for COVID-19. A cross-sectional analysis by Mendez and colleagues (2021) revealed that among 229 patients infected with the SARS-Cov-2 virus, more than half of those experienced moderate impairment in at least one cognitive function, 34 percent of these

patients suffered from impaired verbal fluency, and 6 percent showed impaired working memory performance.

Majority of the studies describing the neurocognitive effects of Covid-19 focus on hospitalized patients, and the mean age of the participants in these studies do not represent the peak of brain development. It has been shown that brain activation and recruitment of different brain regions change significantly with age (Casey et al.,2005). The scope of this thesis aims to investigate how SARS-CoV-2 affects the developing brain in terms of cognitive functions, specifically of working memory and its relationship to psychosis proneness. This thesis hypothesizes that individuals infected with SARS-Cov-2 would perform worse in executive function tasks, specifically verbal fluency and working memory, compared to non-infected controls. In addition, it is expected that infected individuals would show less cortical activation during the working memory task compared to the controls, indicating that Covid-19 infection can be an environmental risk factor.

CHAPTER 2

METHODS

2.1 Participants

The current study involved 76 Turkish native speaking participants between the ages of 14 to 24 (M=17.68, SD=2.50). 34 of the participants are female, and 42 of them are male. The experimental group of participants involved individuals who were infected with SARS-Cov-2 (Covid-19) virus (n=40). The infection status of the participants were confirmed by positive PCR outcome. Individuals who were infected with SARS-Cov-2 and recovered at least two and at most four months before the recruitment, were invited to participate in the research through mailing lists and referrals form Ankara Şehir Hospital, Departments of Child Infection and Child Psychiatry. All participants signed an informed consent. Individuals under the age of 18 were recruited after verbal and written consent from parents or legal guardians. The control group includes individuals who were never knowingly exposed to the SARS-Cov-2 virus. The control data (n=36) came from an earlier study called "Developmental Trajectory of Working Memory Circuits in Adolescent and Young Adult Twins: Cortical maturation, environmental risk, and the implications for schizophrenia and the implications for the vulnerability to psychosis" at Bilkent University (Decision/Meeting No: Decision/Meeting No: 2016_08_02_01-; Project Number: 119k410, PI Toulopoulou). The control data were collected prior to the start of the pandemic between July 2018 and January 2020.

2.2 Behavioral Data

2.2.1 Assessment of Psychosis Proneness

Psychosis proneness is assessed using the Community Assessment of Psychic Experiences Inventory (CAPE) (Stefanis et al., 2002). Participants are asked to complete the inventory in an isolated room. The scale includes three subscales: positive, negative, and depressive. Each subscale involves two dimensions frequency and distress. CAPE-42 has proven to be a valid and reliable scale, all three dimensions correlating with each other and high validity in discriminating different aspects of psychosis proneness (Mark & Toulopoulou, 2016) (Stefanis et al., 2002). Participants completed the revised version of another well-known and validated inventory to assess schizotypy, Structured Interview for Schizotypy-Revised (SIS-R) (Kendler, Lieberman & Walsh, 1989; Vollema & Ormel, 2000). SIS-R includes questions for schizotypal personality traits such as social anxiety, magical ideation, restricted affect, derealization, and depersonalization. Participants were also assessed for psychosis-risk syndromes, using Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2001) administered by a trained psychiatrist. SIPS includes a 19-item severity scale and items that assess the disorganization, positive and negative symptoms of psychosis. SIPS has a high reliability and validity (McGlashan et al., 2001).

2.2.2 Assessment of Environmental Risk Factors

Environmental risk factors are assessed using self-report and structured interview questionnaires. Childhood experience of care and abuse questionnaire (CECA.Q) was used to assess parental loss, physical abuse, neglect and sexual abuse by parents or caregivers before the age of 17 (Bifulco, Bernazzani, Moran & Jacobs, 2005). Ethnicity,

urban birth, use of cannabis and other drugs, paternal age and complications experience by the mother during pregnancy and birth are assessed through structured interview. The aggregated score is calculated for the total environmental risk score (ERS). Intelligence coefficient (IQ) was also investigated as a control variable using Weschler Abbreviated Scale of Intelligence, Second Edition (WASI-II) (Wechsler, 2011). The perceptual reasoning was measured using the block design and matrix reasoning sections of the WASI-II. A composite score was calculated, obtaining a composite perceptual reasoning score.

2.2.3 Assessment of Verbal Fluency

The assessment of verbal fluency included both semantic and phonetic verbal fluency. Semantic verbal fluency task required participants to list as many names as possible belonging to a category in one minute. The categories used in this assessment are "animals" and "fruits". For the phonetic verbal fluency task, participants listed as many names as possible stating with letters "A" and "S" in one minute. Proper names of people and places were excluded during the data analysis. Similarly, repetition of the same word was also excluded from the analysis.

2.3 Cognitive Paradigm

For this study, a well-known and validated working memory task (Tan et al., 2007; Tan et al., 2012) was used. An event-related design was used to prevent the predictability of events in the working memory task. The events in the working memory paradigm consisted of the estimate without working memory (J) in which participants make a numerical judgement without any mathematical computations (e.g 9 vs. 5),

compute/estimate without working memory (C.J.) where participants make a numerical judgement after doing a mathematical computation (e.g. 9-2 vs. 5), estimate after encoding (E_RJ) required participants see two digits and have to memorize these before making a numerical judgement (e.g. 9 vs. 5 followed by a fixation point), in compute/estimate after encoding (E_CJ), participants do a numerical judgement based on the two digits they memorized before the numerical computation, estimate after compute during encoding (CE_RJ) included memorizing the result of the mathematical computation then making a numerical judgement (e.g. 9-2 vs. 5 followed by a fixation point), and control motor task (M) where participants need to press the button on the side that is shown in the screen. For each event, two single digit numbers were displayed on the Telemedicine screen. Participants are asked to make a numerical decision based on the single digit numbers by pressing the buttons, either on the left or the right side. The events were randomized and counterbalanced in terms of appearance so that each event was displayed during the working memory task. The larger and smaller instructions were also randomized and counterbalanced. The numbers on each event were randomly generated. The appearance of the manipulation on the right and left was counterbalanced as well. Accuracy of the participants' answers and reaction times were also recorded as behavioral data.

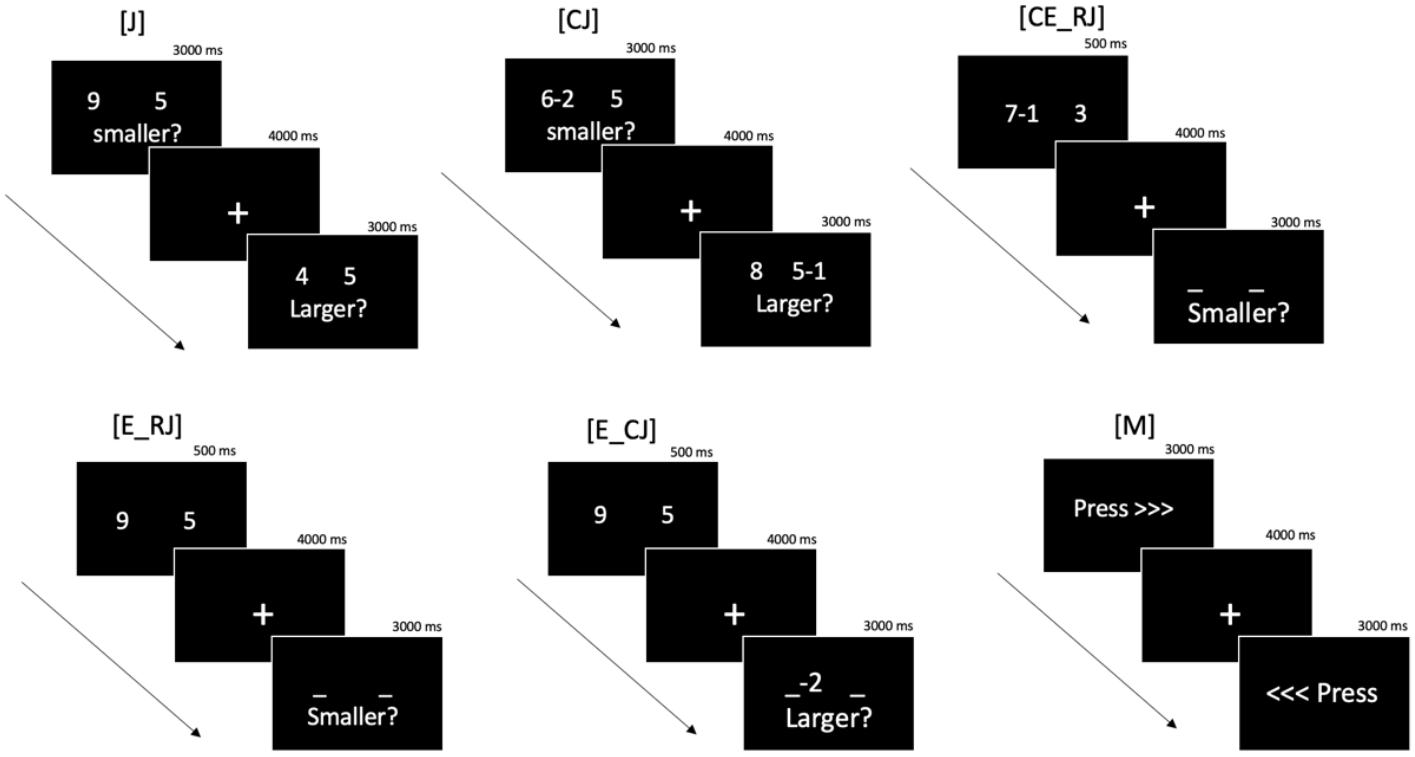


Figure 2.3.1: Demonstration of tasks within the cognitive paradigm. The paradigm contains estimation without working memory (J), computation and estimation without working memory (CJ), estimation after encoding (E_RJ), computation and estimation after encoding (E_CJ), estimation after computation during encoding (CE_RJ), control motor task (M).

2.4 MRI Scanner

A 3-Tesla Siemens Magnetom Trio MRI Scanner is used for the acquisition of the anatomical images and whole brain functional MRI data. A 32-channel head coil was used to apply radio frequency (R.F.) pulses and to provide full brain coverage. While the participants were in the scanner, the stimuli for the working memory task were presented using a telemedicine LCD screen and a mirror placed over the head coil. A fiber optic

response box was used to record the participants' responses onto a Microsoft Excel document.

2.5 Acquisition of Functional Images

BOLD functional data of the whole brain were acquired using T2* weighted echo-planar pulse sequence [T.E. 30 ms, T.R. 2 s]. An ascending interleaved pattern for 24 slices of the whole brain was used. The functional images were acquired while the participants engaged in a working memory task that took 11 minutes and 42 seconds to complete. The trigger signal from the MRI scanner starts the task to synchronize BOLD signal and the onset time of each event in the working memory task.

2.6 Analysis of Functional Images

2.6.1 Preprocessing

Structural and functional magnetic resonance imaging data were stored as raw DICOM files on the MRI scanner console. These files are converted into NIFTI using SPM12 implemented in MATLAB2020a to be able to preprocess the images. Converted NIFTI images for each participant were aligned with the middle volume of the series. Slice time correction was applied to correct for the delays caused by the interleaved slice acquisition. Motion correction is applied to correct for excessive head movement. Due to the nature of voxel size (3.5 mm X 3.5 mm X 5 mm), exclusion criteria for excessive movement are determined as translation larger than 2 mm and rotation larger than 2 degrees deviation from the middle volume (Tan et al., 2007; Tan et al., 2012). 10 of the participants were excluded due to excessive head movement. The functional images were warped to high resolution anatomical images and spatially normalized into MNI

(Montreal Neurological Institute) template and smoothing is applied. Each step of the preprocessing is applied to all participants in the study.

Experimental Condition	Contrasts
Numerical Size Judgement (J – M)	Estimate without Working Memory – Control Motor Task
Numerical Computation outside Working Memory (CJ – J)	Compute without Working Memory – Estimate without Working Memory
Retrieval from Working Memory (E_RJ – M)	Estimate after Encoding – Control Motor Task
Computation in Working Memory (E_CJ – E_RJ)	Compute after Encoding – Estimate after Encoding
Integration of Information within Working Memory (E_CJ – CJ)	Compute after Encoding – Compute without Working Memory
Computation in Encoding (CdE)	Estimate/Compute during Encoding – Estimate after Encoding
Encoding into Working Memory €	Encoding

Table 2.1: Cognitive Subtractions used for each contrast

2.6.2 Statistical Analysis

The functional magnetic resonance imaging data that underwent preprocessing was applied to the General Linear Model using the SPM12 tool in MATLAB2020a. The BOLD response in the entire cortex was analyzed based on the contrasts described above using six different tasks. These contrasts represented the cognitive processes: numerical size judgement (J-M); computation outside working memory (CJ-J); retrieval from working memory (E_RJ-M); numerical computation within working memory (E_CJ-E_RJ); integration of information within working memory (E_CJ-CJ); encoding into

working memory (E) and computation during encoding (CdE). Onset times and accuracy of the answers for each task were extracted from the Microsoft Excel document using a Python script. Correctly performed trials were included in the analysis. For the whole-brain group-level comparison, an independent samples t-test was applied. Activation patterns for each contrast were investigated separately using SPM12. The results for the two-samples t-test analysis were viewed using the xjview toolbox (https://www.alivelearn.net/xjview) on MATLAB R2021b. We investigated the main effect of each contrast and tasks at a threshold of $p<0.001$, a commonly used threshold for fMRI whole brain analysis (Bennet, Wolford & Miller, 2009; Cremers, Wager & Yarkoni, 2017).

A region of interest (ROI) analysis was conducted to investigate the activation differences in the regions associated with working memory. Regions of interest are defined using Brodmann areas predefined in the SPM library. The main ROIs are: right dorsolateral prefrontal cortex Brodmann Area (BA) 46, dorsolateral prefrontal cortex (BA9), and the parietal cortex (BA 40 & 39 &7 (Cieslik et al., 2013; Tan et al., 2012). A mask for the right and left caudate was also used as a region of interest. Earlier research showed signal abnormalities in these regions after exposure to Covid-19 (Kandemirliet al., 2020). For the ROI analysis, the mean activation of two groups was compared.

CHAPTER 3

RESULTS

3.1 Analysis of Demographic Data

No significant age difference was found between the non-infected group (M=18.17, SD=1.96) and the infected group (M=17.25, SD=2.85) as a result of the independent samples t-test ($t(74)=1.61$, $p=0.111$). We also found no significant difference between the gender distribution of the two groups ($X^2(1, N=76)=0.71$, $p=0.68$). No significant difference in intelligence was found between the control group (M=100.93, SD=13.04) and the infected group (M=98.82, SD=13.27) after we conducted an independent samples t-test ($t(69)=0.68$, $p=0.50$).

3.2 Analysis of Behavioral Data

An independent samples t-test was executed to compare the means scores for behavioral assessment. Individuals who were infected with SARS-Cov-2 scored significantly lower in the phonetic category (M=17.15, SD=7.82) when compared to individuals who were not exposed to the virus (M= 21.41, SD=9.45; $t(65)=2.01$, $p<0.05$). In addition, infected individuals scored lower in the semantic category of the verbal fluency test (M=32.43, SD=8.60) in comparison to the non-infected individuals (M=36.60, SD=7.85; $t(64)=2.05$, $p<0.05$). We found no significant difference in CAPE total score between the infected

group (M=74.57, SD=17.34) and non-infected group (M=74.06, SD=15.91) as a result of independent samples t-test ($t(68)=0.57$, $p=0.90$). In addition, CAPE negative, positive and depressive dimension scores did not differ significantly between groups. There was no significant difference between groups in terms of working memory performance.

To further investigate the relationship between psychosis proneness and SARS-Cov-2 infection, we compared scores of two groups for eleven dimensions of SIS-R. Individuals infected with Covid-19 (M=1.46, SD=0.90) scored higher in restricted affect when compared to the non-infected group (M=0.96, SD=0.79; $t(52)=-2.15$, $p<0.05$). In terms of referential thinking, the infected group scored higher on referential thought of being watched (M=1.15, SD=1.16) when compared to the control group (M=0.65, SD=0.77; $t(58)=-2.03$, $p<0.05$).In other dimensions of the SIS-R scale, the groups did not differ significantly. An independent samples t-test was conducted for the total environmental risk factors where two groups did not differ in any subscale for the ERS ($t(53)=-0.53$, $p=0.60$).

Table 3.1.1: Demographics and environmental risk factors

	Control				Covid						
	N	*M*	*SD*	*%*	*N*	*M*	*SD*	*%*	X^2	*F*	*p*
Participants	36				40						
Age		18.17	1.96			17.25	2.85			4.39	.11
Gender									.171		.68
Female	17			47.22	17			42.50			
Male	19			52.78	23			57.50			
Education									3.144		.08
Middle school	10			27.78	16			51.52			
Highschool	26			72.22	17			48.48			
Ethnicity									1.059		.30
Turkish	35			97.22	33			91.67			
Other	1			2.78	3			8.33			
Paternal Age		32.61	5.42			31.89	6.12			1.16	.60
Cannabis									3.877		.14
No exposure	24			85.71	33			3.57			
Moderate exposure	1			3.57	1			2.97			
High exposure	3			10.71	0			0			
Psychosis Proneness									1.471		.48
No proneness				28.57				28.57			
Moderate proneness				54.29				42.86			
High proneness				17.14				28.57			
Years in Urban Upbringing		15.07	3.90			15.97	1.34				

Table 3.2.1: Descriptive statistics and results for behavioral data

	Control			Covid				
	N	*M*	*SD*	*N*	*M*	*SD*	*F*	*p*
Participants	35			35				
CAPE-42								
Total CAPE Score		74.06	15.91		74.57	17.34	.329	.90
Positive Dimension		30.60	6.04		30.09	7.24	1.476	.85
Negative Dimension		28.11	8.37		28.06	7.68	.152	.98
Depressive dimension		13.71	3.73		14.97	4.91	2.777	.23
Verbal Fluency								
Phonetic		21.41	9.45		17.15	7.82	.837	.05*
Semantic		36.59	7.85		32.44	8.59	.010	.04*
Working memory performance		87.92	6.14		84.87	9.42	2.766	.11
Perceptual Reasoning Composite Score		100.94	13.04		98.82	13.27	.006	.50

*:p<0.05, **:p<0.01

Table 3.2.2: Descriptive Statistics and results for SIS-R scores

	Control			Covid			
	N	*M*	*SD*	*N*	*M*	*SD*	*F*	*p*
Participants	34			26				
Social Isolation		.47	.61		.81	.90	1.448	.09
Introversion		.74	.86		1.04	.92	.004	.19
Hypersensitivity		1.26	.93		1.23	1.07	1.99	.90
Referential Thinking (Being watched)		.65	.77		1.15	1.16	9.85	**.05***
Referential Thinking (Being talked about)		1.06	.60		1.15	.92	11.89	.63
Suspiciousness		1.35	.69		1.56	.71	.000	.27
Restricted Affect		.91	.75		1.46	.90	2.496	**.01***
Magical Ideation		1.11	.84		1.13	.80	.000	.97
Illusions		1.06	.60		1.36	.75	6.773	.09
Psychotic Phenomena		.74	.75		.96	.91	.794	.31
Derealization/Depersonalization		.24	.61		.31	.62	.587	.65
Missing				2				

*:p<0.05, **:p<0.01

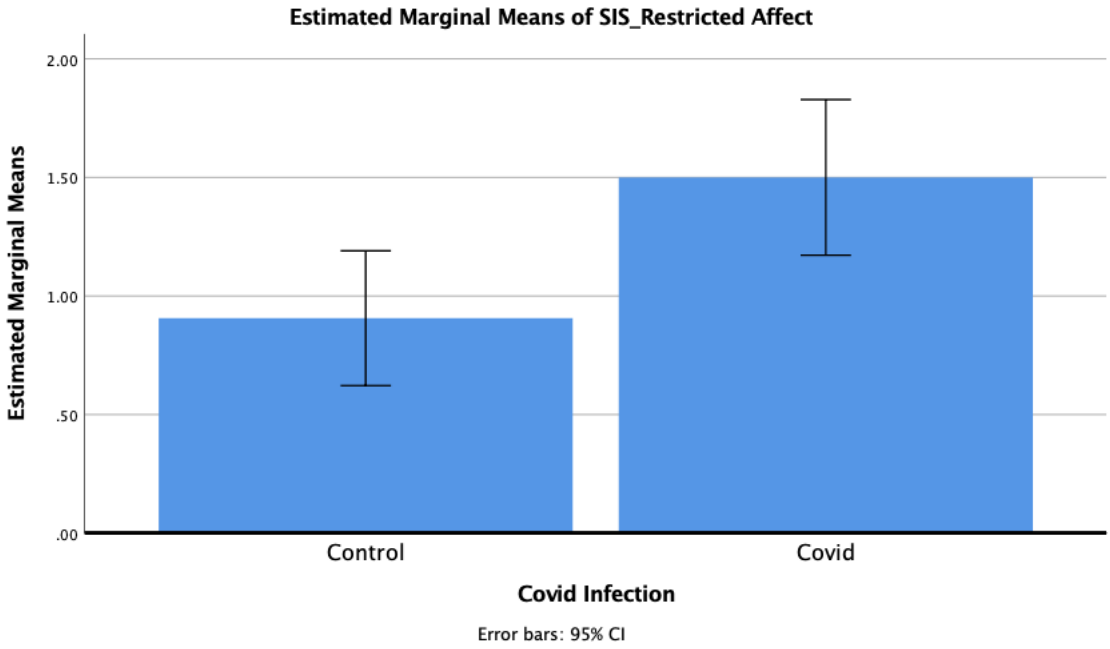


Figure 3.2.1: The comparative bar chart illustrates the SIS-Restricted Affect Scores between two groups

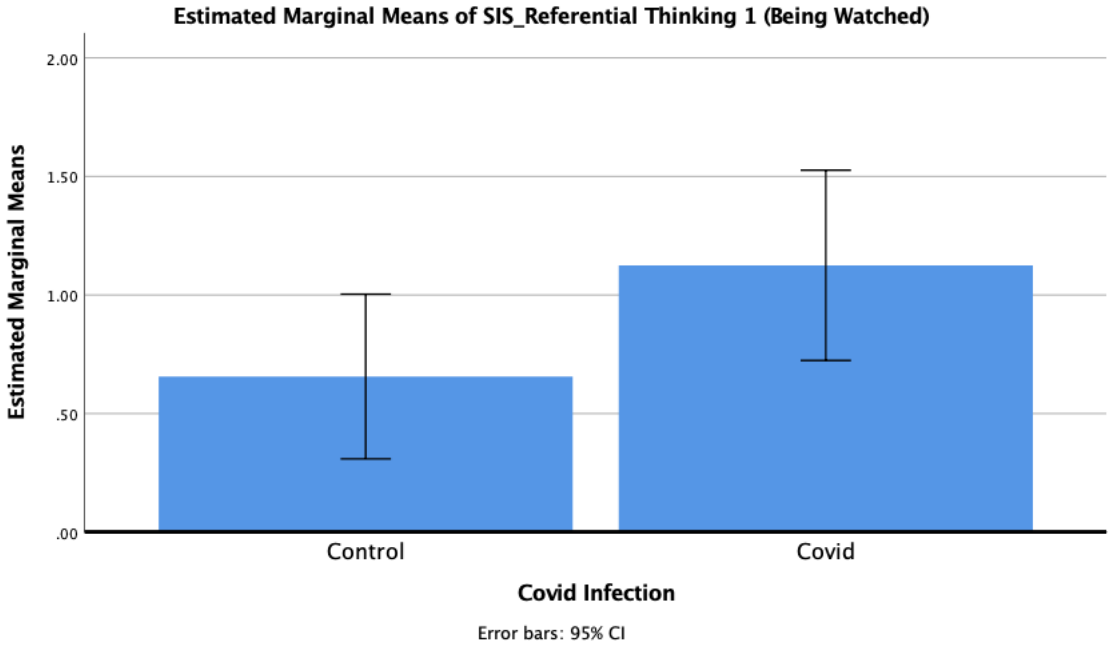


Figure 3.2.2: The comparative bar chart illustrates the SIS-Referential Thinking (Being Watched) Scores between two groups

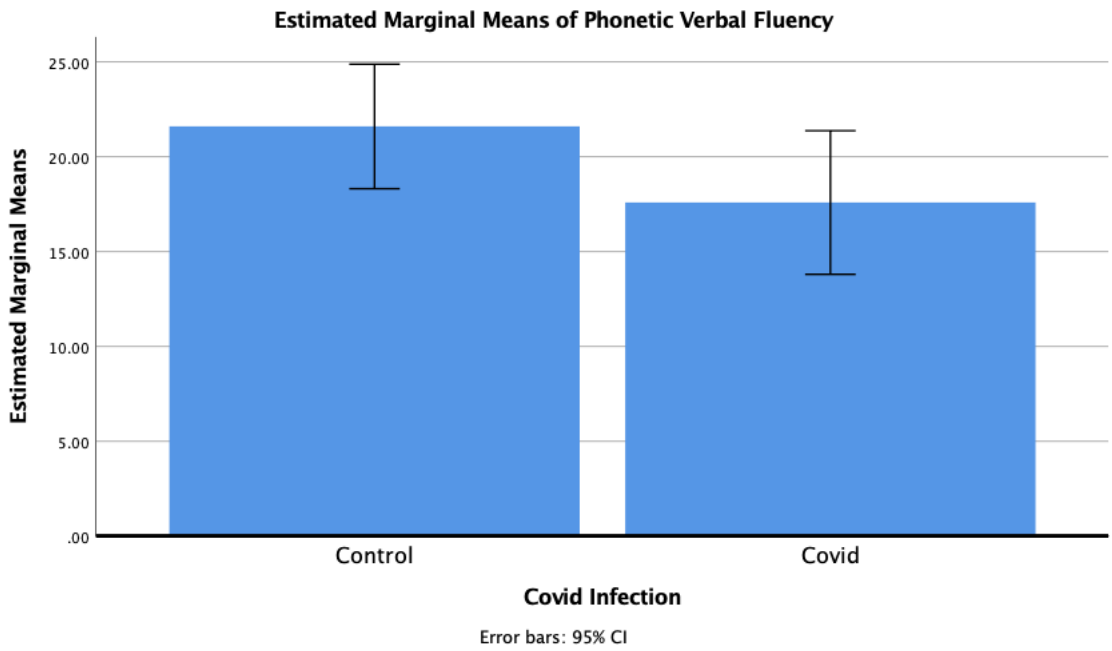


Figure 3.2.3: The comparative plot demonstrates phonetic verbal fluency scores between two groups

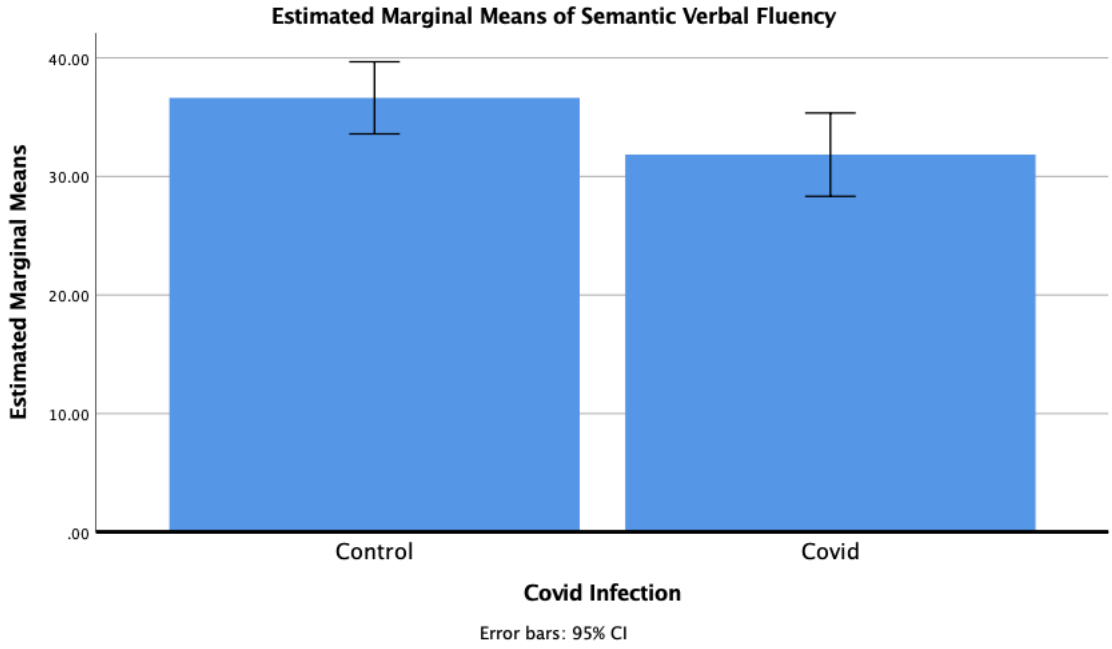


Figure 3.2.4: The comparative plot demonstrates the semantic verbal fluency scores between two groups

3.3 Task-Based Activation Results

In order to investigate differences in activation during the working memory task between two groups (infected with SARS-Cov-2 vs. non-infected), an unpaired two-samples t-test was conducted for each contrast. During numerical size judgment (J-M contrast), individuals who were not exposed to the SARS-Cov-2 virus showed greater activation in the parietal region when compared to the individuals who were infected (peak 34 -38 50; $t=3.59$, $p<0.001$, uncorrected). In addition, greater activation in the right temporal region was associated with numerical size judgment in the control group (peak 62 -24 -10; $t=3.81$, $p<0.001$). No significant differences were found for activation during computation without working memory across groups (CJ-J contrast). During retrieval from working memory (E_RJ-M contrast), greater activation in the inferior parietal region was seen in individuals who were not infected when compared to individuals who were exposed to SARS-Cov-2 (peak 42 -34 32; $t=3.30$, $p<0.001$, uncorrected). During numerical computation in working memory (E_CJ-E_RJ contrast), activation patterns did not differ significantly across groups. Manipulation of information in working memory (E_CJ-CJ contrast) was associated with greater activation in the left parietal region in the control group when compared to the group exposed to the virus (peak -52 -52 44; $t=3.41$, $p<0.001$). During encoding (E), the control group showed greater activation in the left medial frontal gyrus when compared to the infected group (peak -4 8 52, $t=3.51$, $p<0.001$, uncorrected).

We further investigated activation differences across individual tasks. During estimation without working memory task (J), greater activation in the medial frontal gyrus was seen in the control group when compared to the infected group (peak -4 8 52; $t=3.55$,

p<0.001, uncorr.). In addition, greater activation in the middle temporal gyrus in the control group was associated with the estimation without working memory task (peak 58 -20 -14; t=3.41, p<0.001). During computation and estimation without working memory (CJ task), greater activation in the middle frontal gyrus was seen in the control group when compared to the infected group (peak -36 12 32; t=3.91, p<0.001). Similarly, computation and estimation after encoding (E_CJ task) is associated to greater activation in the left middle frontal gyrus in the control group when compared to the infected group (peak -42 10 32; t=3.81, p<0.001). In addition, greater activation is associated to encoding in the left temporal region in the control group compared to the infected group (peak -22 -66 18; t=3.43, p<0.001). Computation during encoding (CdE) was associated to greater activation in the middle frontal gyrus in the control group when compared to the infected group (peak -32 12 34; t=4.24, p<0.001, uncorrected).

The region of interest analysis revealed that during manipulation of information in working memory, activation in the prefrontal cortex (BA9) did not differ across groups (t(60)=0.20, SD=2.65, p=0.84). Activation difference across groups during encoding in the left caudate (t(59)=1.82, SD=0.96, p=0.07) and the right caudate were not significant (t(59)=1.43, SD=0.87, p=0.16). On the other hand, integration of information within working memory is associated with increased activation in the prefrontal cortex in the control group compared to the infected group (BA9) (t(60)=2.53, SD=1.86, p=0.01). The ROI analysis also revealed that during retrieval of information from working memory, activation patterns did not differ significantly in the parietal region (BA 39&40) (t(60)=1.50, SD=1.52, p=0.14).

To control for the effect of environmental risk factors, analysis of covariance was conducted. We found that, there is a significant effect of Covid-19 infection on activation during numerical size judgment controlling for paternal age, $F(1,55)= 13.0.5$, $p=0.001$, ethnicity, $F(1,55)=12.31$, $p=0.001$, cannabis exposure, $F(1,49)=8.69$, $p=0.005$, and years of urban upbringing, $F(1,49)=20.14$, $p<0.001$. Covariance analysis revealed that there was a significant effect of infection on retrieval from working memory when we controlled for paternal age, $F(1,55)=4.57$, $p=0.04$, ethnicity, $F(1,55)=5.44$, $p=0.02$, cannabis exposure, $F(1,49)=5.54$, $p=0.02$, and years of urban upbringing, $F(1,49)=9.21$, $p=0.004$. We also found a significant effect of infection on computation during encoding when we controlled for environmental risk factors, $F(1,34)=7.97$, $p=0.008$.

In order to investigate whether the differences in activation during working memory between the groups reflect the difference in verbal fluency performance, we conducted a linear regression analysis. We found that performance in semantic verbal fluency significantly predicted activation in computation during encoding, $F(1,59)=4.19$, $p<0.05$.

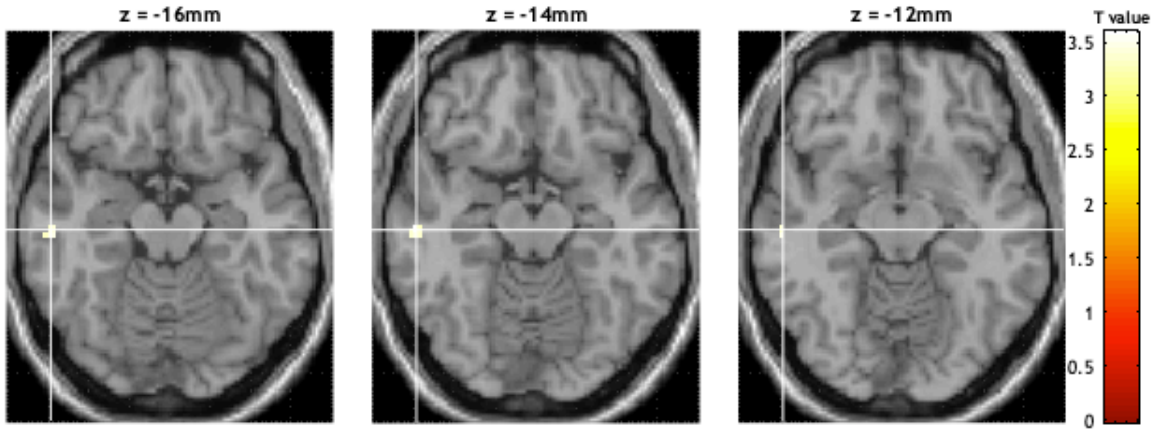


Figure 3.3.1: Increased activation in the right middle temporal gyrus in the control group during estimation without working memory (J task)

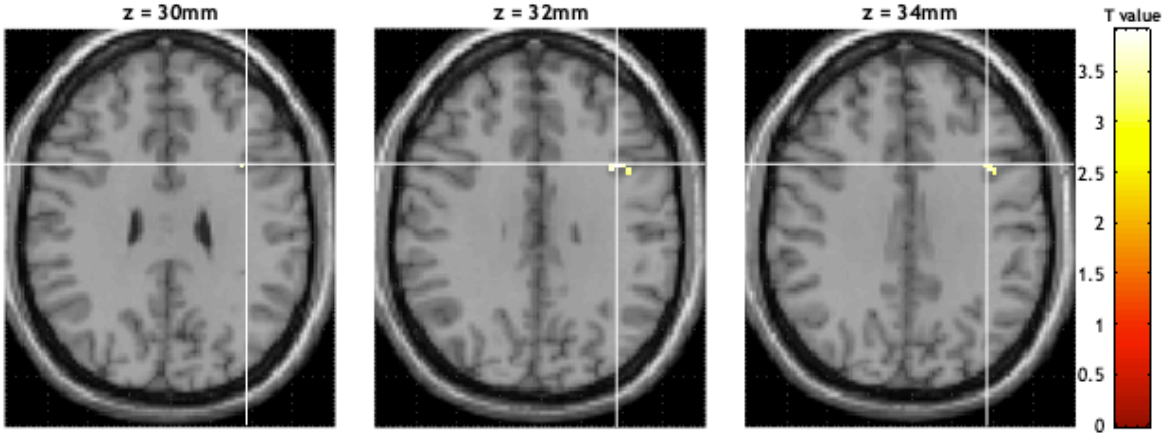


Figure 3.3.2: Increased activation in the middle frontal gyrus in the control group during computation and estimation without working memory (CJ task)

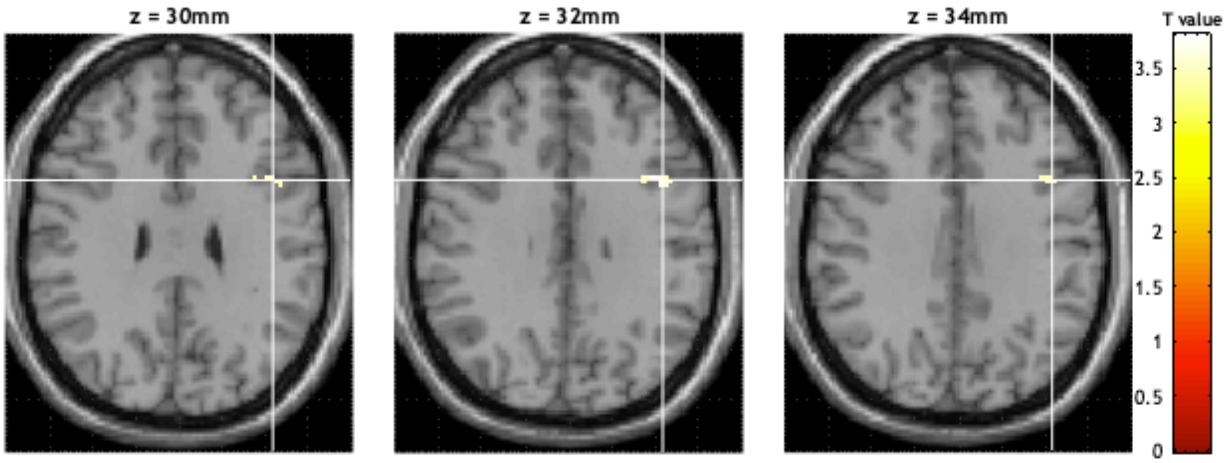


Figure 3.3.3: Increased activation in the left middle frontal gyrus during computation and estimation after encoding (E_CJ task) in the control group

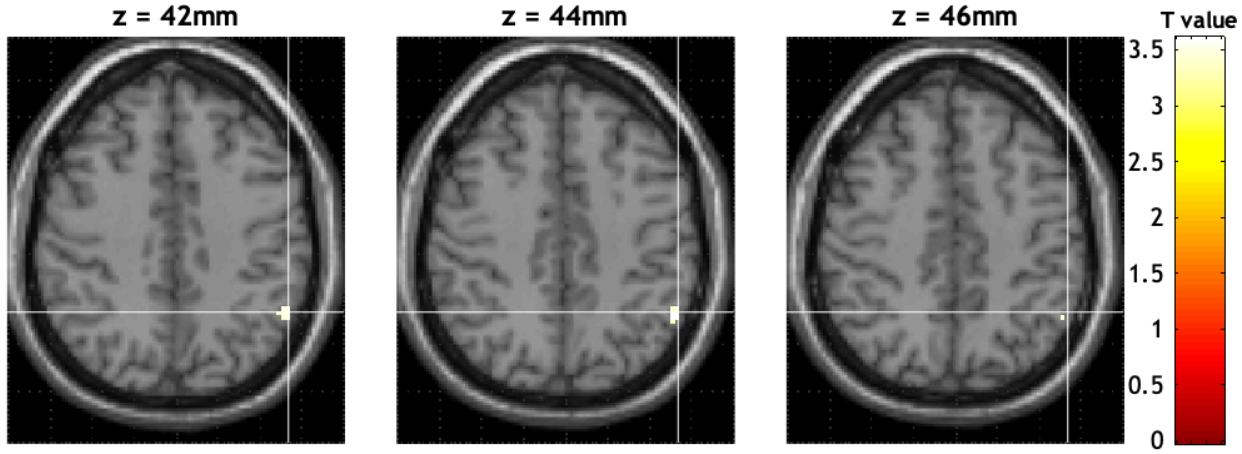


Figure 3.3.4: Increased activation in the inferior parietal lobule in controls during manipulation of information in working memory (E_CJ-CJ contrast)

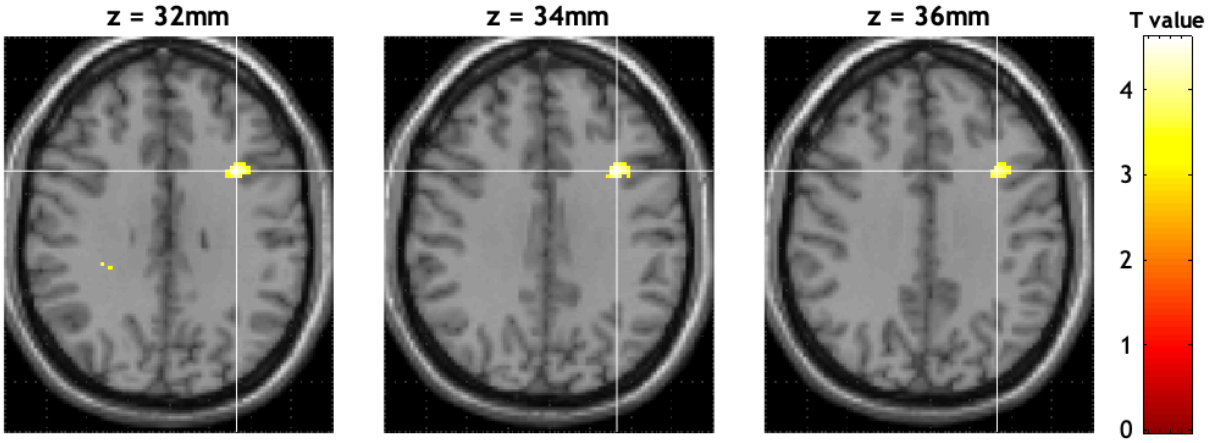


Figure 3.3.5: Increased activation in the middle frontal gyrus in individuals who are not exposed to SARS-Cov-2 when compared to control participants during computation during encoding (CdE contrast)

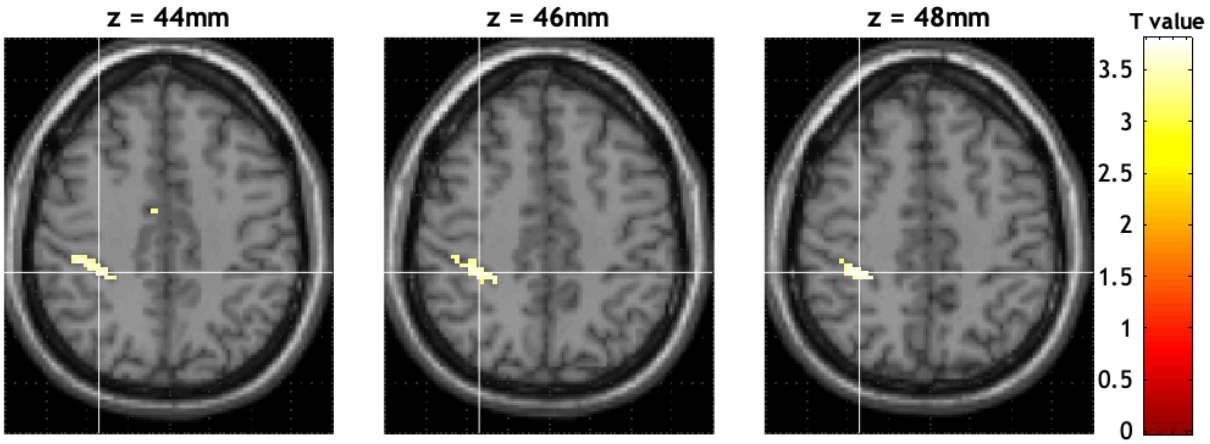


Figure 3.3.6: Greater activation in inferior parietal lobule in individuals who were not exposed to SARS-Cov-2 in numerical size judgement outside working memory (J-M contrast

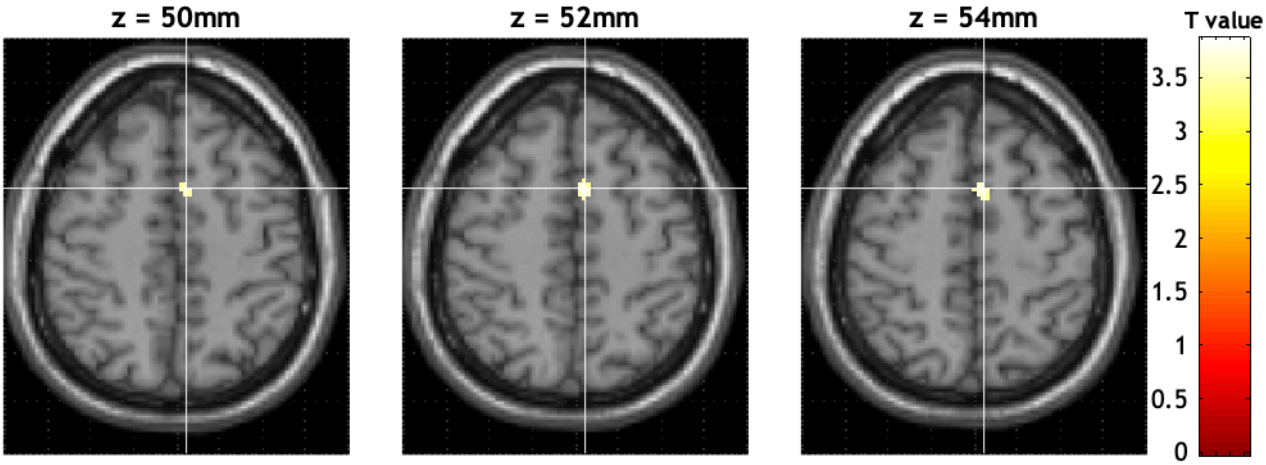


Figure 3.3.7: Greater activation in the medial frontal gyrus associated to encoding of information in the control participants (E task)

Table 3.3: Peak coordinates and results for Working Memory Task

Contrast		x	y	z	t	P
Numerical Size Judgement	Control>Covid	34	-38	50	3.81	<0.001
	Control>Covid	62	-24	-10	3.81	<0.001
Retrieval from Working Memory	Control>Covid	42	-34	32	3.30	<0.001
Manipulation of Information in Working Memory	Control>Covid	-52	-52	44	3.41	<0.001
Encoding	Control>Covid	-4	8	52	3.51	<0.001
Computation During Encoding	Control>Covid	-32	12	34	4.24	<0.001

CHAPTER 4

CONCLUSION AND DISCUSSION

This thesis aimed to explore whether individuals exposed to the SARS-Cov-2 virus in the peak period of brain development, between the ages of 14 and 23, have altered brain activation patterns during a working memory task in the regions known to be critical in executive function, such as the dorsolateral prefrontal cortex, parietal lobule, and the basal ganglia. Earlier research showed signal abnormalities in these regions after exposure to Covid-19 (Kandemirliet al., 2020). A secondary aim was to inspect whether there is an association between exposure to the virus and psychosis proneness. We predicted that individuals infected with SARS-Cov-2 would have lower performance in executive functions such as verbal fluency and working memory and lower brain activation across several working memory tasks.

Previous studies have found that individuals infected with the SARS-Cov-2 virus experienced cognitive impairment and psychotic-like symptoms in addition to the clinical features of Covid-19 such as fatigue, brain fog, and respiratory system failure (Hellmuth et al., 2021; Mendez et al., 2021). Even though there is evidence that Covid-19 could lead to cognitive impairment and be a risk factor for psychosis, previous studies focused on hospitalized and middle-aged individuals. We aimed to present

evidence that the infection could be a risk for the developing brain, thus, we focused on non-hospitalized adolescents and young adults.

Building on previous work investigating the psychological and neurological effects of Covid-19, in the scope of this thesis, we aimed to investigate whether Covid-19 infection could be an environmental risk factor in the emergence of psychosis. To present evidence, we investigated brain activation under functional magnetic resonance imaging during a well-known working memory task. We measured cognitive impairment using a simple yet effective task, verbal fluency test that requires executive function. In addition, we also investigated other environmental factors of psychosis such as ethnicity, paternal age, and years of urban upbringing. The psychosis proneness of participants was measured using reliable and valid measures such as CAPE-42 and SIS-R.

After conducting functional magnetic resonance imaging, we found activation differences in the middle frontal gyrus, medial temporal region, prefrontal cortex, and parietal region. Despite the shortage of studies focusing on task-based functional imaging, previous studies have found signal abnormalities and hypometabolism in these regions after the infection (Hosp et al., 2020; Kandemirli et al., 2020; Kremer et al., 2020.) We found that individuals exposed to the virus showed decreased brain activation in tasks requiring numerical size judgment, computation, and manipulation compared to those who were never exposed to the virus. Although we did not find a significant difference between groups for working memory performance, this could be related to the design of the task. The working memory task is designed to measure the cortical

activation as much as possible, thus merely pointing out the activation differences rather than performance (Tan et al., 2007).

Although groups did not differ in intelligence, we found that individuals exposed to the SARS-Cov-2 virus performed worse in both phonetic and semantic categories of the verbal fluency task, and performance in verbal fluency is correlated with cortical activation during working memory. Similarly, Mendenz and colleagues (2021) revealed that after infection, a significant percentage of the patients showed impairment in verbal fluency. Zhou and colleagues (2020) investigated the effects of Covid-19 on cognitive functioning in recovered patients using several cognitive tasks measuring attention, memory function, executive function, and perception. They found that even after recovery, Covid-19 infection affects cognitive functioning.

Parra and colleagues (2020) indicated that the most prevalent symptoms after Covid-19 infection were delusions, prejudice, and referential beliefs. They reported that the manifestation of these symptoms could correspond to a secondary psychotic episode because of the absence of predisposing factors such as a family history of severe mental illness, and substance abuse. Similarly, in the current study, although the environmental risk factors of psychosis, such as cannabis use, paternal age, and urban upbringing, did not differ across groups, individuals who were infected scored higher in restricted affect and referential thoughts of being watched. Even though the two groups did not differ significantly in terms of positive, negative and depressive symptomatology for psychosis proneness, the difference between groups in restricted affect and referential thoughts should be approached with caution.

In previous literature, exposure to a virus is related to increased psychosis proneness. There are several explanations for the relationship. There is evidence that the changes in the genetic expression that increase the psychosis risk also led to changes in the blood-brain barrier permeability, thus inducing increased vulnerability of the brain tissue to the virus. Another related explanation is that an infection that affects the central nervous system by affecting the synthesis of proteins related to schizophrenia, such as the N-methyl-D-aspartate receptor, could increase the risk for psychosis (Kepinska et al., 2020). In addition, it has been stated that the altered gene expression underlying psychosis and schizophrenia might lead to a decreased ability of the blood-brain barrier to isolate the virus, thus harming the central nervous system. Post-mortem studies revealed signal intensity abnormalities in regions critical for executive function (Kandemirli et al., 2020). Kremer and colleagues (2020) found that the most frequent signal intensity abnormalities were located in the middle temporal lobe after infection with Covid-19. We also found that infected participants had decreased activation in the middle temporal gyrus during numerical size judgment.

On the other hand, Hosp and colleagues (2021) have stated that the cognitive decline experienced by Covid-19 patients might not be due to cortical damage but might be related to hypometabolism in the frontoparietal regions. In addition, Zhou and colleagues (2020) indicated that the cognitive impairment in the recovered Covid-19 patients is significantly correlated to the CRP level, the protein which signals inflammation in the body. These findings suggest that the inflammatory reaction is closely related to both functional and structural damage to the brain and contributes to understanding the effects of a disease that has worldwide effects.

The current study investigated the changes in the developing brain due to Covid-19 infection by focusing on adolescents and young adults, using functional magnetic resonance imaging. To our knowledge, most of the literature focused on structural changes in hospitalized older adults. Several studies center on behavioral data, whereas our study focuses on neuroimaging data which can broaden the knowledge about the changes in the brain after infection. In addition, we examined more than one cognitive function and included environmental risk factors for psychosis proneness.

The current study also has limitations. The small number of participants due to the strict exclusion criteria and the case-control design of the study makes it difficult to draw a strong causal relationship between Covid-19 and psychosis. It needs to be pointed out that there is still a need for further investigation to discover the direction of the relationship between Covid-19 infection and psychosis proneness. Future research might need to explore how high genetic risk and Covid-19 infection interact when explaining psychosis risk by investigating healthy relatives of individuals diagnosed with psychosis.

To conclude, the current thesis investigated whether Covid-19 infection could be a risk factor for psychosis in the period of brain development. We investigated whether infection is associated to activation changes in the brain and executive function performance in addition to psychosis proneness in individuals between the ages of 14 and 23. The current study revealed that infection is related to activation changes in the regions associated with working memory such as prefrontal cortex, medial frontal gyrus, medial temporal gyrus, and inferior parietal lobule. Covid-19 infection was also

associated to lower verbal fluency performance and higher psychotic-like experiences. The findings of this thesis are in line with previous research pointing out that Covid-19 could pose a risk for later conversion to psychosis.

REFERENCES

Arciniegas, D. B. (2015). Psychosis. *Continuum: Lifelong Learning in Neurology*, *21*(3 Behavioral Neurology and Neuropsychiatry), 715.

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). *The principled control of false positives in neuroimaging. Social Cognitive and Affective Neuroscience, 4(4), 417–422.*

Bentall, R. P., de Sousa, P., Varese, F., Wickham, S., Sitko, K., Haarmans, M., & Read, J. (2014). From adversity to psychosis: pathways and mechanisms from specific adversities to specific symptoms. *Social psychiatry and psychiatric epidemiology*, *49*(7), 1011-1022.

Benros, M. E., & Mortensen, P. B. (2019). Role of infection, autoimmunity, atopic disorders, and the immune system in schizophrenia: evidence from epidemiological and genetic studies. *Neuroinflammation and Schizophrenia*, 141-159.

Bifulco, A., Bernazzani, O., Moran, P. M., & Jacobs, C. (2005). The childhood experience of care and abuse questionnaire (CECA.Q): Validation in a community series. *British Journal of Clinical Psychology* 44: 1-20.

Boisgueheneuc, F. d., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., … Dubois, B. (2006). *Functions of the left superior frontal gyrus in humans: a lesion study. Brain, 129(12), 3315–3328.*

Bourque, F., van der Ven, E., & Malla, A. (2011). A meta-analysis of the risk for psychotic disorders among first-and second-generation immigrants. *Psychological medicine*, *41*(5), 897-910.

Brown, E., Gray, R., Monaco, S. L., O'Donoghue, B., Nelson, B., Thompson, A., Francey, S., & McGorry, P. (2020). The potential impact of COVID-19 on psychosis: a rapid review of contemporary epidemic and pandemic research. *Schizophrenia research*, *222*, 79-87.

Casey, B. J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: what have we learned about cognitive development?. *Trends in cognitive sciences*, *9*(3), 104-110.

Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: a review. *Frontiers in psychology*, *9*, 401.

Cieslik, E. C., Zilles, K., Caspers, S., Roski, C., Kellermann, T. S., Jakobs, O., … Eickhoff, S. B. (2012). Is There "One" DLPFC in Cognitive Action Control? Evidence for Heterogeneity From Co-Activation-Based Parcellation. *Cerebral Cortex, 23*(11), 2677–2689.

Comer, A. L., Carrier, M., Tremblay, M. È., & Cruz-Martín, A. (2020). The inflamed brain in schizophrenia: the convergence of genetic and environmental risk factors that lead to uncontrolled neuroinflammation. *Frontiers in Cellular Neuroscience*, *14*, 274.

Coolen, T., Lolli, V., Sadeghi, N., Rovai, A., Trotta, N., Taccone, F. S., ... & De Tiège, X. (2020). *Early postmortem brain MRI findings in COVID-19 non-survivors. Neurology, 95*(14), 2016-2027.

Cremers, H. R., Wager, T. D., & Yarkoni, T. (2017). *The relation between statistical power and inference in fMRI. PLOS ONE, 12(11), e0184923.*

Dean, K., & Murray, R. M. (2022). Environmental risk factors for psychosis. *Dialogues in clinical neuroscience*.

Demjaha, A., Valmaggia, L., Stahl, D., Byrne, M., & McGuire, P. (2012). Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. *Schizophrenia bulletin*, *38*(2), 351-359.

Debost, J. C., Larsen, J. T., Munk-Olsen, T., Mortensen, P. B., Agerbo, E., & Petersen, L. V. (2019). Childhood infections and schizophrenia: The impact of parental SES and mental illness, and childhood adversities. *Brain, behavior, and immunity*, 81, 341-347.

Ferrando, S. J., Klepacz, L., Lynch, S., Tavakkoli, M., Dornbush, R., Baharani, R., ... & Bartell, A. (2020). COVID-19 Psychosis: A potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response?. Psychosomatics.

Fett, A. K. J., Lemmers-Jansen, I. L., & Krabbendam, L. (2019). Psychosis and urbanicity: a review of the recent literature from epidemiology to neurourbanism. *Current opinion in psychiatry*, *32*(3), 232.

Fischer, D., Threlkeld, Z. D., Bodien, Y. G., Kirsch, J. E., Huang, S. Y., Schaefer, P. W., ... & Edlow, B. L. (2020). Intact brain network function in an unresponsive patient with COVID-19. *Annals of Neurology, 88*(4), 851-854.

Hartwig, F. P., Borges, M. C., Horta, B. L., Bowden, J., & Smith, G. D. (2017). Inflammatory biomarkers and risk of schizophrenia: a 2-sample mendelian randomization study. *JAMA psychiatry*, *74*(12), 1226-1233.

Hellmuth, J., Barnett, T. A., Asken, B. M., Kelly, J. D., Torres, L., Stephens, M. L., ... & Peluso, M. J. (2021). Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. Journal of NeuroVirology, *27*(1), 191-195.

Holper, L., Aleksandrowicz, A., Müller, M., Ajdacic-Gross, V., Haker, H., Fallgatter, A. J., Hagenmuller, F., Rössler, W., & Kawohl, W. (2015). Brain correlates of verbal fluency in subthreshold psychosis assessed by functional near-infrared spectroscopy. *Schizophrenia Research*, *168*(1–2), 23–29.

Horan, W. P., Reise, S. P., Subotnik, K. L., Ventura, J., & Nuechterlein, K. H. (2008). The validity of Psychosis Proneness Scales as vulnerability indicators in recent-onset schizophrenia patients. *Schizophrenia research*, *100*(1-3), 224–236.

Hosp, J. A., Dressing, A., Blazhenets, G., Bormann, T., Rau, A., Schwabenland, M., ... & Meyer, P. T. (2021). Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. Brain.

Huang, A. S., Rogers, B. P., Anticevic, A., Blackford, J. U., Heckers, S., & Woodward, N. D. (2019). Brain function during stages of working memory in schizophrenia and psychotic bipolar disorder. Neuropsychopharmacology, *44*(12), 2136-2142.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet, *395*(10223), 497–506.

Iqbal, Y., Al Abdulla, M. A., Albrahim, S., Latoo, J., Kumar, R., & Haddad, P. M. (2020). Psychiatric presentation of patients with acute SARS-CoV-2 infection: a retrospective review of 50 consecutive patients seen by a consultation-liaison psychiatry team. *BJPsych Open*, *6*(5).

Kandemirli, S. G., Dogan, L., Sarikaya, Z. T., Kara, S., Akinci, C., Kaya, D., … Kocer, N. (2020). Brain MRI findings in patients in the intensive care unit with COVID-19 infection. Radiology, 297(1), E232–E235.

Kendler, K. S., Lieberman, J. A., & Walsh, D. (1989). The Structured Interview for Schizotypy (SIS): a preliminary report. *Schizophrenia bulletin*, *15*(4), 559-571.

Kępińska, A. P., Iyegbe, C. O., Vernon, A. C., Yolken, R., Murray, R. M., & Pollak, T. A. (2020). Schizophrenia and influenza at the centenary of the 1918-1919 Spanish influenza pandemic: mechanisms of psychosis risk. Frontiers in Psychiatry, 11, 72.

Kremer, S., Lersy, F., de Sèze, J., Ferré, J. C., Maamar, A., Carsin-Nicol, B., ... & SFNR-COVID Group. (2020). Brain MRI findings in severe COVID-19: a retrospective observational study. Radiology, *297*(2), E242-E251.

McGlashan, T. H., Walsh, B. C., Woods, S. W., Addington, J., Cadenhead, K., Cannon, T., & Walker, E. (2001). Structured interview for psychosis-risk syndromes. *New Haven, CT: Yale School of Medicine*.

Manoach, D. S., Gollub, R. L., Benson, E. S., Searl, M. M., Goff, D. C., Halpern, E., ... & Rauch, S. L. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. Biological psychiatry, *48*(2), 99-109.

Leanza, L., Egloff, L., Studerus, E., Andreou, C., Heitz, U., Ittig, S., Beck, K., Uttinger, M., & Riecher-Rössler, A. (2018). The relationship between negative symptoms and cognitive functioning in patients at clinical high risk for psychosis. *Psychiatry Research*, *268*, 21–27.

Mark, W., & Toulopoulou, T. (2016). Psychometric properties of "community assessment of psychic experiences": review and meta-analyses. *Schizophrenia Bulletin*, *42*(1), 34-44.

Meijer, J. H., Schmitz, N., Nieman, D. H., Becker, H. E., van Amelsvoort, T. A. M. J., Dingemans, P. M., Linszen, D. H., & de Haan, L. (2011). Semantic fluency deficits and reduced grey matter before transition to psychosis: A voxelwise correlational analysis. *Psychiatry Research - Neuroimaging*, *194*(1), 1–6.

Parra, A., Juanes, A., Losada, C. P., Álvarez-Sesmero, S., Santana, V. D., Martí, I., ... & Rentero, D. (2020). Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. Psychiatry research, 291, 113254.

Pukrop, R., Ruhrmann, S., Schultze-Lutter, F., Bechdolf, A., Brockhaus-Dumke, A., & Klosterkötter, J. (2007). Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophrenia research*, *92*(1-3), 116-125.

Reichenberg, A. (2005). Cognitive impairment as a risk factor for psychosis. *Dialogues in clinical neuroscience*, *7*(1), 31.

Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., ... & David, A. S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry*, *7*(7), 611-627.

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in psychology*, *5*, 772.

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Evdokimidis, I. K., Stefanis, C. N., Verdoux, H., & Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological medicine*, *32*(2), 347.

Stilo, S. A., & Murray, R. M. (2019). Non-genetic factors in schizophrenia. *Current psychiatry reports*, *21*(10), 1-10.

Tan, H. Y., Chen, Q., Goldberg, T. E., Mattay, V. S., Meyer-Lindenberg, A., Weinberger, D. R., & Callicott, J. H. (2007). Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal- striatal brain systems during arithmetic and temporal transformations in working memory. *Journal of Neuroscience*, *27*(49), 13393–13401.

Tan, H. Y., Chen, A. G., Kolachana, B., Apud, J. A., Mattay, V. S., Callicott, J. H., Chen, Q., & Weinberger, D. R. (2012). Effective connectivity of AKT1-mediated dopaminergic working memory networks and pharmacogenetics of anti-dopaminergic treatment. *Brain*, *135*(5).

Torales, J., O'Higgins, M., Castaldelli-Maia, J. M., & Ventriglio, A. (2020). The outbreak of COVID-19 coronavirus and its impact on global mental health. *International Journal of Social Psychiatry, 66*(4), 317–320.

Toulopoulou, T., Zhang, X., Cherny, S., Dickinson, D., Berman, K. F., Straub, R. E., ... & Weinberger, D. R. (2019). Polygenic risk score increases schizophrenia liability through cognition-relevant pathways. *Brain*, *142*(2), 471-485.

Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, behavior, and immunity*, *87*, 34-39.

Trutti, A. C., Verschooren, S., Forstmann, B. U., & Boag, R. J. (2021). Understanding subprocesses of working memory through the lens of model-based cognitive neuroscience. *Current Opinion in Behavioral Sciences*, *38*, 57-65.

Vollema, M. G., & Ormel, J. (2000). The reliability of the structured interview for schizotypy-revised. *Schizophrenia bulletin*, *26*(3), 619-629.

Wechsler, D. (2011). Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II) San Antonio. *TX: Pearson.*

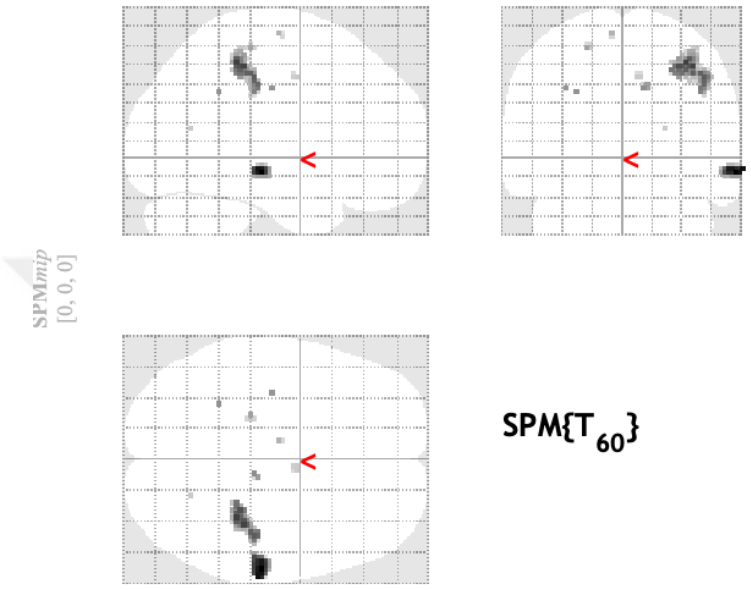
Zhang, R., Picchioni, M., Allen, P., & Toulopoulou, T. (2016). Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies. *Schizophrenia Bulletin*, *42*(4), 1068–1077.

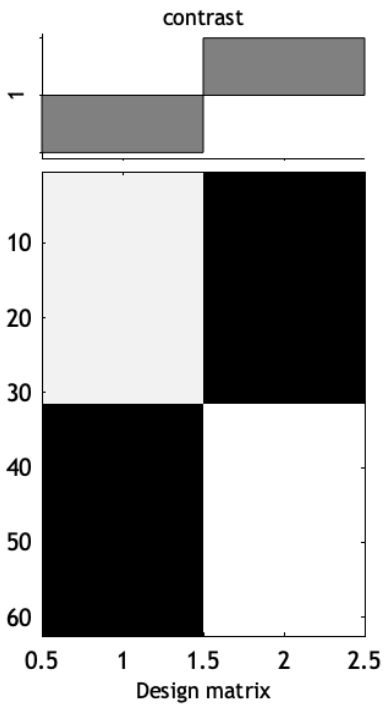
Zhou, H., Lu, S., Chen, J., Wei, N., Wang, D., Lyu, H., Shi, C., Hu, S., (2020). The landscape of cognitive function in recovered COVID-19 patients. *Juarnal of Psychiatric Reseacrh, 129, 98-102.*

Zulkifli, N. A., Sivapatham, S., & Guan, N. C. (2020). Brief psychotic disorder in relation to coronavirus, COVID-19 outbreaks: a case report. Malaysian Journal of Psychiatry, *29*(1).

APPENDIX

[J-M]Con>Cov



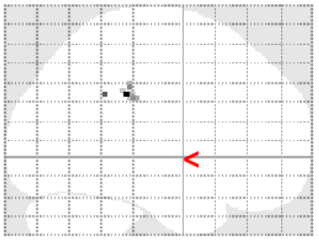


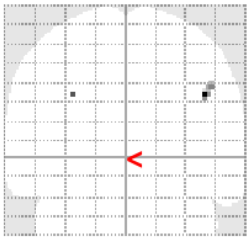
SPMresults: ./Contrasts-2nd_Level/J-M
Height threshold T = 3.231709 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

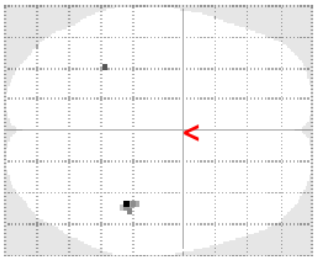
set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.018	9	0.259	0.349	69	0.078	0.395	0.691	4.07	3.81	0.000	62 -24 -10
		0.033	0.077	175	0.009	0.631	0.691	3.81	3.59	0.000	34 -38 50
						0.724	0.691	3.71	3.50	0.000	44 -28 42
		0.916	0.859	5	0.641	0.857	0.711	3.54	3.36	0.000	10 -28 36
		0.964	0.859	1	0.859	0.871	0.711	3.51	3.34	0.000	-28 -48 34
		0.964	0.859	1	0.859	0.876	0.711	3.51	3.33	0.000	-34 -18 36
		0.904	0.859	6	0.605	0.899	0.711	3.47	3.30	0.000	-22 -30 58
		0.940	0.859	3	0.729	0.932	0.780	3.40	3.24	0.001	-8 -14 66
		0.916	0.859	5	0.641	0.959	0.843	3.32	3.17	0.001	6 -4 42
		0.964	0.859	1	0.859	0.962	0.843	3.31	3.16	0.001	22 -64 14

[E_RJ-M]Con>Cov

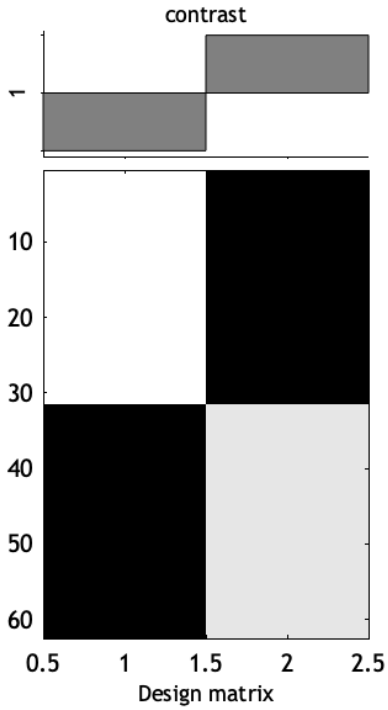




SPM*mip*
[0, 0, 0]



SPM{T_{60}}

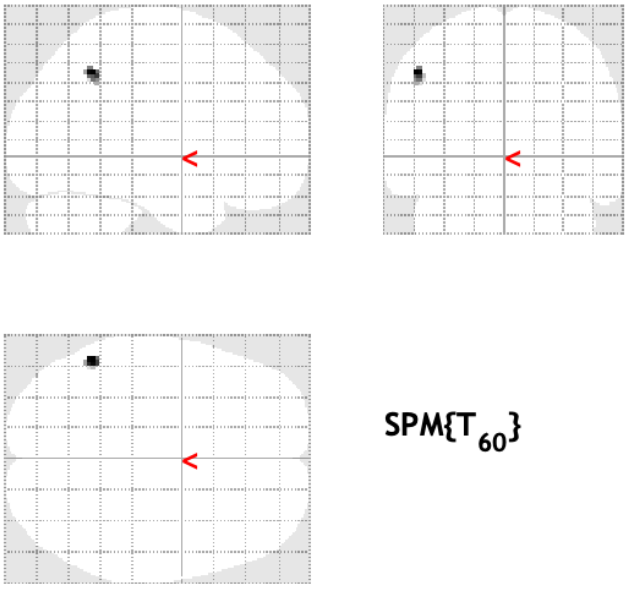


SPMresults: ./Contrasts-2nd_Level/E_RJ-M
Height threshold T = 3.231709 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

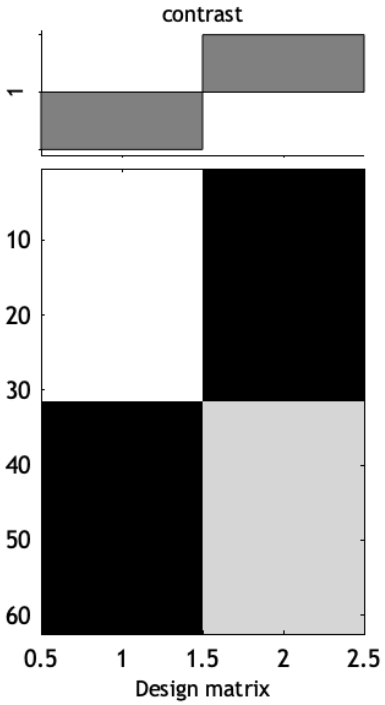
Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.896	2	0.825	0.860	12	0.453	0.893	0.819	3.47	3.30	0.000	42 -34 32
		0.963	0.860	1	0.860	0.937	0.819	3.38	3.22	0.001	-32 -46 32

[E_CJ-CJ]Con>Cov



$SPM\{T_{60}\}$

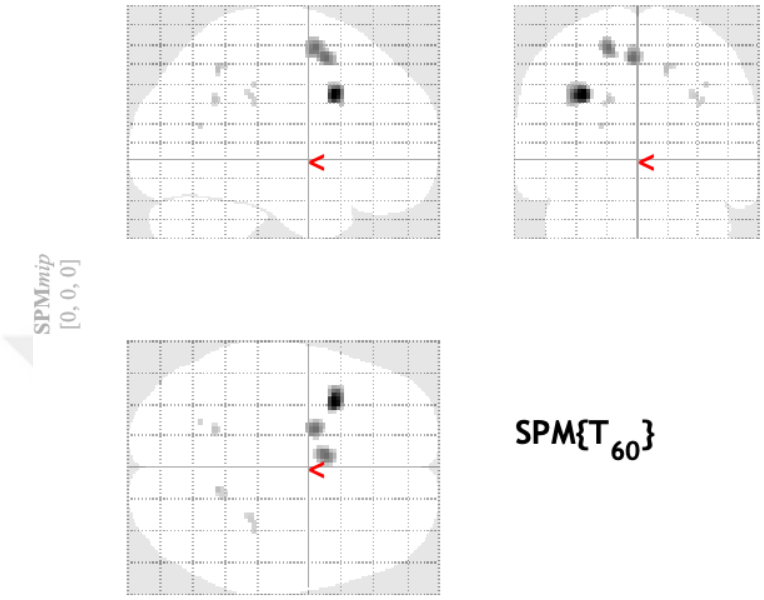


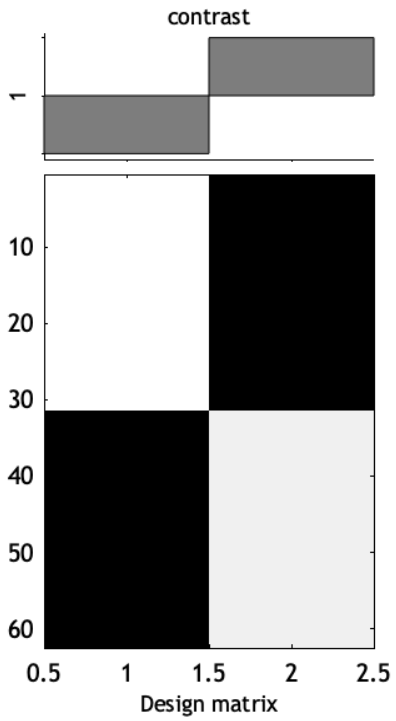
SPMresults: ./Contrasts-2nd_Level/E_CJ-CJ
Height threshold T = 3.231709 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

cluster-level				peak-level					mm mm mm
$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}	
0.670	0.389	22	0.389	0.705	0.429	3.60	3.41	0.000	-52 -52 44

[CdE]Con>Cov



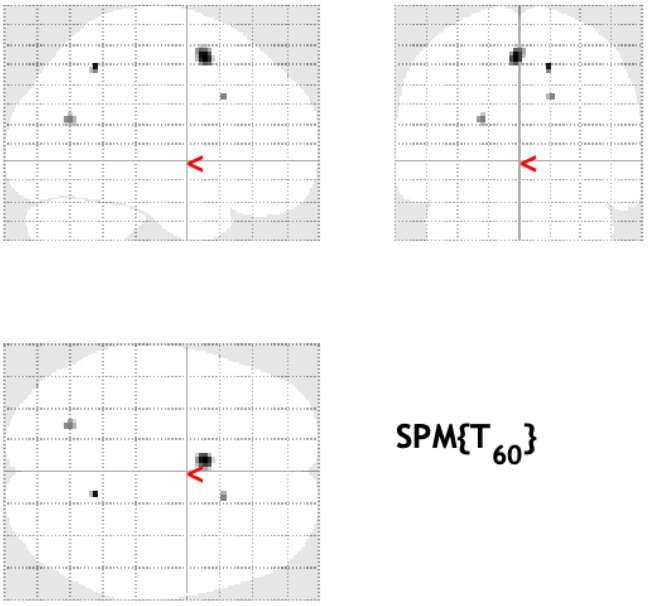


SPMresults: ./Task Based 2ndLevel/CdE
Height threshold T = 3.231709 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

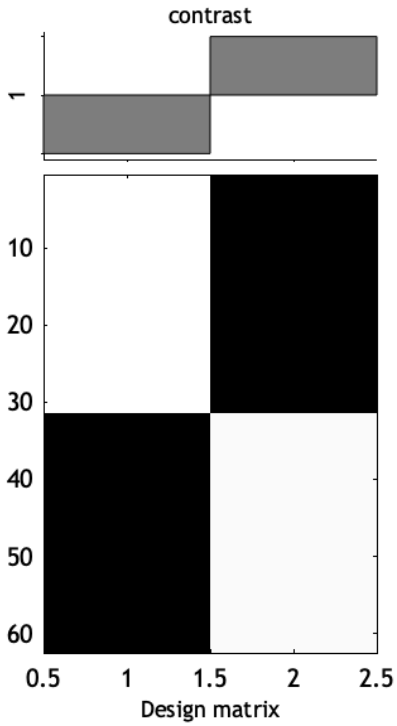
Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.008	9	0.199	0.438	89	0.066	0.031	0.085	4.97	4.53	0.000	-32 12 32
		0.388	0.438	53	0.146	0.345	0.380	4.08	3.82	0.000	-18 2 58
		0.340	0.438	60	0.124	0.346	0.380	4.08	3.81	0.000	-4 8 52
		0.857	0.872	8	0.579	0.866	0.816	3.46	3.29	0.000	14 -52 46
		0.895	0.872	5	0.671	0.889	0.816	3.42	3.26	0.001	-18 -54 30
		0.920	0.872	3	0.753	0.911	0.816	3.38	3.22	0.001	30 -34 32
		0.947	0.872	1	0.872	0.929	0.816	3.34	3.19	0.001	-22 -62 16
		0.947	0.872	1	0.872	0.935	0.816	3.33	3.17	0.001	36 -32 38
		0.933	0.872	2	0.805	0.936	0.816	3.32	3.17	0.001	34 -32 30

[E]Con>Cov



SPM{T_{60}}



SPMresults: ./Task Based 2ndLevel/Encoding
Height threshold T = 3.231709 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_E)	p_{uncorr}	
0.398	4	0.489	0.812	41	0.209	0.516	0.548	3.86	3.63	0.000	-4 8 52
		0.913	0.812	3	0.761	0.585	0.548	3.78	3.57	0.000	14 -52 48
		0.837	0.812	9	0.566	0.829	0.574	3.50	3.32	0.000	-22 -66 20
		0.926	0.812	2	0.812	0.841	0.574	3.48	3.31	0.000	16 18 32