

ARITHMETIC AND TEMPORAL TRANSFORMATIONS OF WORKING MEMORY ACTIVATION IN SUBJECTS PRONE TO PSYCHOSIS

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF ENGINEERING AND SCIENCE
OF BILKENT UNIVERSITY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF
MASTER OF SCIENCE
IN
NEUROSCIENCE

By
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September 2018

Arithmetic and Temporal Transformations of Working Memory Activation in Subjects Prone to Psychosis

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

ARITHMETIC AND TEMPORAL TRANSFORMATIONS OF WORKING MEMORY ACTIVATION IN SUBJECTS PRONE TO PSYCHOSIS

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M.S. in Neuroscience

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September 2018

Working memory (WM) deficit is a well-studied cognitive impairment in psychosis which is stemming from various developmental abnormalities containing neurobiological heterogeneity. Recently, many studies have concluded that the WM impairment is a symptom which manifests itself before the onset of the disorder, but these studies mostly focused on the individuals at clinically high risk. The mild proneness to psychosis which develops during the adolescent period is not well understood and how the working memory is affected due to mild proneness to psychosis has not been elucidated heretofore. In this research, we aimed to examine the association between the mild proneness to psychosis and working memory processing. Thirty-two individuals were split in half as mildly prone to psychosis and not prone to psychosis based on the Structured Interview for Schizotypy (SIS-R). Each participant performed a robust working memory task which consists of computational and temporally varying information loads. The data were collected via a magnetic resonance imaging (MRI) scanner and analysed by applying a general linear model to detect altered working memory activations due to proneness to psychosis. We have observed that the processes requiring manipulation and rapid updating of the information are associated with a large network of prefrontal cortex and superior parietal lobule. The finding of this study suggests that the mild proneness to psychosis has affected the working memory weakly and that the alterations demonstrated in the prefrontal cortex and parietal lobules may be clinically relevant to psychosis.

Keywords: Working Memory, Psychosis, fMRI.

ÖZET

PSİKOZA YATKIN BİREYLERDE ÇALIŞMA BELLEĞİ AKTİVASYONUNUN ARIŞMETİK VE ZAMANA BAĞLI DÖNÜŞÜMLERİ

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Eylül 2018

Çalışma belleği eksikliği, nörobiyolojik kökeni heterojen olan çeşitli gelişimsel bozukluklardan kaynaklanan psikoza görülen iyi çalışılmış bir bilişsel bozukluktur. Yakın dönemde yapılan birçok araştırma, çalışma belleğindeki bozulmanın, hastalığın başlangıcından önce kendini gösteren bir semptom olduğu sonucuna varmıştır. Fakat, bu çalışmaların birçoğu klinik olarak yüksek risk altında olan bireylere odaklanmıştır. Ergenlik dönemi boyunca gelişen psikoza olan hafif yatkınlık iyi anlaşılamamış ve buna bağlı olarak çalışma belleğinin nasıl etkilendiği bugüne kadar açığa çıkarılamamıştır. Bu çalışmada biz, çalışma belleği süreci ile psikoza olan hafif yatkınlığın arasındaki ilişkiyi incelemeyi amaçladık. Otuz iki birey, şizotip için yapılandırılmış bir değerlendirmeye dayanarak hafifçe yatkın olanlar ve yatkın olmayanlar olarak iki gruba ayrılmıştır. Her katılımcı, içerisinde hesaba dayalı ve zamana bağlı olarak değişen bilgiler içeren çalışma belleği testini tamamlarken davranışsal verileri kaydedilmiştir. Fizyolojik veriler ise, bir manyetik rezonans görüntüleme cihazı aracılığıyla toplanmış olup psikoza yatkınlığa bağlı olarak değişmiş çalışma belleği aktivasyonlarını tespit edebilmek adına bir genel doğrusal model uygulanarak analiz edilmiştir. Manipülasyon ve hızlı güncelleme gerektiren bilgi işleme süreçlerinin, prefrontal korteks ve üst pariyetal lobdaki geniş bir ağ ile ilişkili olduğunu gözlemledik. Bu çalışmada elde edilen bulgular, psikoza olan hafif yatkınlığın çalışma belleğini zayıf bir şekilde etkilediğini ve prefrontal kortekste ve pariyetal lobda ortaya konan dönüşümlerin psikoz ile klinik olarak ilişkili olabileceğini göstermektedir.

Anahtar sözcükler: Çalışma Belleği, Psikoz, iMRG.

Acknowledgement

First of all, I would like to thank **Timothea Touloupoulou** for giving me the chance of being a part of her research group. She has been a great sounding board for my ideas and she was always there for me to help with her kindness.

I am deeply indebted to **Hulusi Kafalıgönül** for his wholehearted help without hesitation in the path of this thesis. I am genuinely thankful to **Metehan Çiçek** for accepting to be a reader and his understanding in helping me get through all of the red tapes.

With all my soul, I would like to specially thank **Benay Başkurt**, who warm the clockes of my hearth with her smile and helped me through my stressful times. This thesis would have never been possible without her.

Kübra Çelikbaş and **Rabia Şen** are friends long before they became my colleagues. I would like to thank them for being great friends a guy could ask for.

Finally, I am thankful to **Pelin Kasap** who was a dedicated co-worker in the data collection of this thesis and also **Mehmet Günay** for being such a great flatmate.

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Chapter 1

Introduction

1.1 Working Memory: A Brief Overview

Working memory (WM) is one part of the executive control system which forms a basis for cognitive processes varying from selective attention to specific stimuli to complex activities such as decision-making [1]. Especially, WM plays a key role in the maintenance of information for a brief period providing later access and even manipulation on held information [2]. The information held in WM could be both auditory or visual based on the form of maintenance by which the phonological loop (e.g. promoting language comprehension) or the visuospatial sketchpad (e.g. promoting visuospatial reasoning). Each of these subsystems demonstrated by behavioural methods is controlled by an attentionally restricted gatekeeper which eliminates auditory or visual stimuli for maintenance and manipulation [2]. It is worth noting that, this central executive is an attentional controller rather than a memory system. Because the duration of attention is restricted due to individual differences and executive functioning varies with normally ageing brain. For instance, in older nonimpaired adults, WM load impairments associated with the number of items they can selectively hold in the system at any given time were demonstrated by Mattay et al. and Nyberg et al [3, 4].

In the past years, various behavioural tasks were developed by scientists to demonstrate a quantitative scale of memory duration. These tasks include an encoding phase where the participants are expected to hold the presented information (e.g. digits, letters or photographs). What the task measures during the encoding phase is either a selective attention (i.e., focusing on a certain property of the stimuli such as the size of the digits) or a divided attention (i.e. focusing on more than one property of the stimuli such as size and manipulation) [2]. One of the most commonly used and well-defined measurement method is the " n -back task". In this type of tasks, the participants are imposed to a series of stimuli during encoding phase and after that in the following response phase, they are asked to decide whether the stimuli displayed during the response phase matches with the stimuli presented in the encoding phase [5]. Only the correct responses are taken into account to reflect the measurement of WM capacity. The reason why the n -task widely preferred is the capability of forcing the participants' central executive limits by dividing attention (e.g. focusing on multiple features such as size judgement and manipulation) and allowing the simultaneous measurement by online displaying on the screen [5].

The regions correlated with working memory activation in the brain is defined by the neuroimaging techniques developed in the last decades. The noninvasive functional magnetic resonance imaging (fMRI) and the technique which uses radioactive isotopes to detect activated regions the positron emission tomography (PET) are widely used in this field to depict specifically activated regions during a WM task. The researches conducted in the past years has shown that the prefrontal cortex (PFC), parietal lobule, cingulate gyrus and subcortical regions such as hippocampus are related with WM processing in healthy young adults [6]. Furthermore, the researches which use n -back tasks showed that the required activation for the task completion is revealed on the dorsolateral PFC, ventrolateral PFC, rostral PFC, posterior parietal cortex and premotor cortex [5]. These techniques have made a huge impact on the development of human studies and they allow to investigate the altered brain activations throughout the brain between the experimental groups.

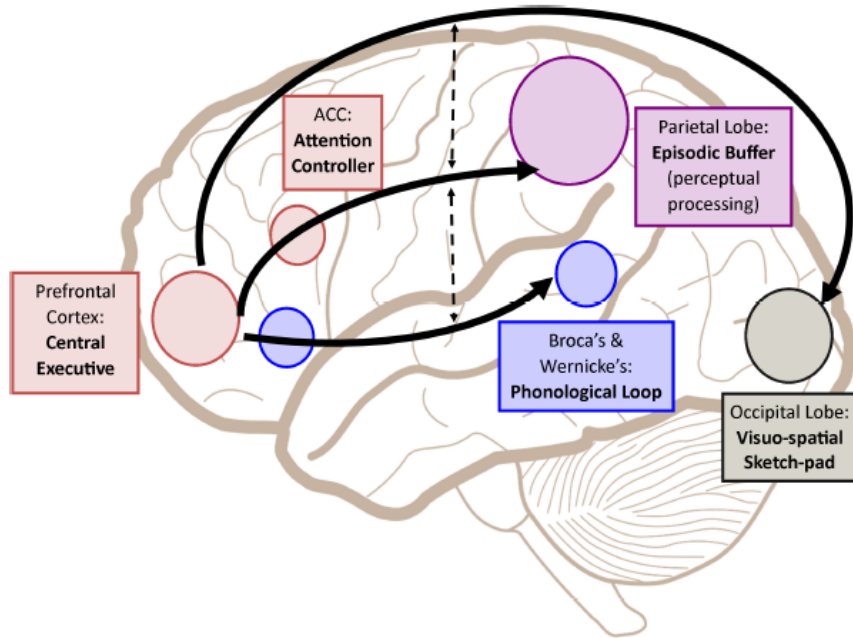


Figure 1.1: An illustration of the multicomponent working memory model proposed by Baddeley, 2010 [7] from the study of Chai et al. [8]. Even though, the contemporary view of neuroscience is a holistic approach, depicting the model of Baddeley is giving an overview of working memory processing.

1.2 The Regions Associated with Working Memory

1.2.1 The Role of Prefrontal Cortex in Working Memory

After years of research conducted in this field, researchers come to an agreement that the encoded information during the working memory task is associated with PFC [9, 10, 11]. This consensus also evolved over time and the researchers revealed that the strong neural activity which represents the working memory processes in PFC occurs during the period between the encoding phase and the response phase in the WM task [12, 13, 14, 15]. The distinctive property of this period is being ideally isolated from the other information processes in the brain [16] and only including the recalled stimulus represented in working memory task [17, 18]. Evidences for this remarkable period is not only limited to the human neuroimaging researches, the experiments conducted in the other primates to measure the single-neuron activity level have been also showed the same properties [19, 20, 21]. In the single-neuron activity recordings, even though the monkeys were distracted by another stimuli during this period, it is shown that the information held in WM was preserved [17]. The neuroimaging techniques developed in the last decades was used to test whether the PFC in humans is activated during this period as well and similarly, a considerable increase in PFC was observed. In a spatial working memory study, the lateral PFC still maintained its activation even after several seconds delay of presented stimuli [19].

If the PFC is responsible from the activation caused by working memory load during the delay period, a damage occurred in PFC should lead to working memory impairment. The various lesion studies in monkeys as well as in humans were performed to prove it and the results confirmed that the proposed idea was true both in monkeys [12, 14, 15, 22, 23] and humans [24, 25, 26]. A microstimulation study also showed that a small effect in the WM circuitry during the delay period resulting with a raise in the number of incorrect responses [27]. Additionally, a coherent observation with the definition of working memory was performed, when

the duration of the delay period was increased, the number of incorrect responses was also accordingly increased as expected. The researches aforementioned were supportive for the widely accepted view of PFC is the location where the recalled information of WM processed. On the other hand, a considerable amount of publication was generated which approach with suspicion to prevailing opinion [28, 29, 30, 31, 32, 33, 34].

1.2.2 The Other Regions Associated with Working Memory Processing

Along with the PFC, the working memory processing is highly correlated with the parietal cortex. Superior parietal cortex has been widely seen as the executive perspective of working memory [35, 36] and is considered as the administrative centre of selective attentional control [37]. There has been an interesting finding suggesting that the working memory capacity is associated with parietal cortex activity. When the number of items to remember increases until 3-4 items accordingly the activity of parietal cortex also increase. Even though it is not a critical region for the working memory processing, one of the regions which is activated in most working memory tasks is the cerebellum [38]. In the recent years, the number of evidence supporting the role of the cerebellum in verbal rehearsal has been increased, but perhaps it may have a more general role in working memory processing [39].

The prevalent view of the involvement of basal ganglia in working memory processing has been revealed by various neuroimaging studies to data [40] and it is a fundamental structure for computational models [41]. More specifically, the involvement of striatal (a nucleus in the subcortical basal ganglia) has been demonstrated with the lesion studies in human [26] and the decreased working memory performance corresponding to fMRI BOLD signal and the finding of dopaminergic signalling alteration in the striatum in Parkinson's disease patients [42]. In the early times of debates on the distinction between short-term memory

and long term memory, an important finding in the patients with medial temporal lobe (MTL) resection was asserted suggesting that despite even though had crucially impaired long-term memory, there was no abnormality in the short-term processing. Hence, the MTL was not considered as important for working memory. However, the advances in neuroimaging studies have revealed that MTL is activated in working memory tasks [43] and recently, it has been thought as the MTL could be related with binding and relational processes included in working memory [44]. The research conducted on connectivity during a delayed-response task was in accord with the idea of working memory is an emergent property of the dynamic interactions of various brain areas and it has been shown that the activity in sensory areas is linked to the activity in PFC, parietal cortex, striatum, and also the MTL [45].

1.3 Disrupted Working Memory Circuitry in Adolescent Psychosis

Various researches conducted to understand the complexity of the psychosis, particularly schizophrenia (SZ), have been concluded with that it is a neurodevelopmental disorder [46, 47, 48, 49, 50, 51]. On the other hand, the adolescence brain which undergoes this critical neurodevelopmental period is barely understood. The adult SZ patients were studied using WM tasks to investigate the aberrant activity in the brain, but the adolescent brain still needs to further examination. One of the well-recognized and reliable symptom of SZ is impairment in WM [52, 53, 54, 55, 56]. This declined cognitive ability was observed in healthy relatives of SZ patients [57, 58, 59] and also subjects at the high-risk group as well [60, 61, 62, 63, 64]. Moreover, impairment in WM was also reported as a reliable indicator to follow the progress of diagnosed psychosis [65, 66].

The network distributed between the regions the dorsolateral prefrontal cortex (dlPFC) and the parietal lobule as being responsible from the WM circuitry was

demonstrated many times by various researches [29, 67, 68, 69, 70, 71]. Furthermore, the key roles of the anterior cingulate cortex (ACC) and left frontal lobule in WM circuitry were also shown [72]. An important conclusion came up from a study with SZ subjects, the decreased communication between the frontal lobule and hippocampal regions was in parallel with decreased accuracy in WM task. [73].

It is worth to emphasize that the adolescent brain undergoes highly active rearrangement in the developmental period and the studies with adult SZ patient mostly neglects this fact [74, 75, 76, 77]. For instance, it has been found that when the healthy adolescent subjects got older, the communication between the regions frontal lobule and parietal which are responsible from WM processes strengthened [78]. Another study also has shown that WM capacity occurring in those regions is also positively correlated with age [79]. In contrast to these evidences, the ageing is associated with reduced activity in the regions of the superior frontal, superior parietal [80] and limbic cingulate gyrus [78] as well. Even though these contradictory results, the adolescent brain shapes in a well-organized manner while approaching to late stage of adolescence [81] and suggesting that WM circuitry refinement and PFC maturation with increasing age are correlated [74, 77, 82].

The subjects diagnosed with psychosis during adolescent period could be particularly enlightening due to the developmental nature of the disorder [83]. The adolescent psychosis (AP) patients compared to the adult patients at the onset of the disorder show more severe cognitive deficits, especially in the field of WM [84, 85]. Therefore, the adolescent brain development carries a considerable importance to solve the underlying neural and cognitive mechanism of the psychosis. In this respect, further researches needed to be conducted with the adolescent brain to develop new insights into the disorder.

The neuroimaging researches conducted with AP subjects to date have demonstrated that the frontal lobule and ACC which are associated with high-level processing in the brain build aberrant mutual signalling patterns with prefrontal, limbic and visual regions compared to healthy subjects [86, 87, 88, 89, 90, 91].

Additionally, if the WM capacity is not assigned as a regressor in the analysis, it is possible to suggest that AP subjects have weaker connectivity among the dlPFC and the other WM related regions such as ACC [89]. The same study also surprisingly concluded with that while the ageing is negatively correlated with the activation in PFC as expected, but the connectivity level between dlPFC and ACC was increasing, inferring that the signal transmission along the network gets worse in the late stage of adolescence period [89]. Another study has found that if the WM capacity which varies among the subjects is assigned as a regressor, in the late phase of the delay period, decreased WM capacity compared to healthy subjects was a reflection of increased neural activation [91]. The inconsistency among the studies on underlying mechanisms of WM processes shows that the WM impairment in AP, especially the variability of WM capacity among subjects, still needs to be enlightened.

1.4 Classifying individuals at risk for psychosis

The WM impairment is a well-established indicator for proneness to psychosis [92] and the behavioural results in WM tasks has corroborated that in subjects at risk-level before developing the disorder [93, 94]. It has been evidenced that the subjects at the high-risk level for psychosis have weaker activations in the regions of the prefrontal and parietal cortices during WM task relative to healthy subjects [95, 96].

The studies conducted to date have converged to a common understanding that proneness to psychosis leads to developing miscommunication between frontal and temporal regions during WM processing [97]. All the data collected from the healthy, at the high-risk level and first episode psychosis subjects were concluded with the growing body of evidence [98]. The subjects at the high-risk level bear a resemblance to diagnosed psychosis subjects in the aberrant anatomy [99, 100] and functionality [101] of the brain and also the disturbed biochemical processes in micro-universe [102, 103], but less severe [104]. Importantly, it has been shown that the aberrant function of prefrontal regions in WM processes is emerged due

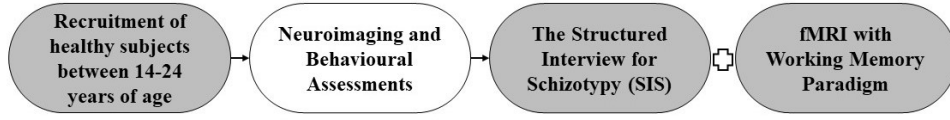


Figure 1.2: The experiment outline.

to the grey matter impairment in subjects at the high-risk level [105]. Even though there are plenty of studies which show the dysfunctional connectivity of these regions in WM processes, using these abnormalities as a diagnosis tool for high-risk level of psychosis is not trustworthy.

The diagnosis of the subjects at high-risk level of psychosis are based on the criteria of various screening tools such as the PACE (Personal Assessment and Crisis Evaluation Clinic), the CAPE (The Community Assessment of Psychic Experience) or SIS-R (Structured Interview for Schizotypy-Revised). Among those, if the subjects have a family history of psychosis and exhibit remarkable decrease in cognitive performance, the PACE is reliable tool to classify the subjects as psychotic [106]. However, the consistency rate for transition to the first episode of psychosis in 2 years is only 29% [107] and after 3-10 years is 35 [108]-49% [109]. The SIS-R was designated to measure the schizotypal symptoms by collecting the data from the relatives of schizophrenia. The purpose of the assessment is identifying the milder forms of symptoms, therefore its usage in clinical field is limited [110]. Since the population considered in the scope of this thesis is the mildly prone to psychosis individuals, the SIS-R was preferred to determine the risk level of the subjects.

In the scope of this thesis, we investigated whether the proneness to psychosis has an impact on alterations of the brain activation during the process of working memory. To test the hypothesis, we have identified 16 subjects who are mildly prone to psychosis based on the SIS-R assessment. For the control group, 16 subjects who have not proneness to psychosis also identified based on the same assessment. All of these participants were between 14 and 24 years old. The working memory task that we use was a well-established paradigm and it was based on computational and temporally varying information loads.

Chapter 2

Methods

2.1 Participants

This study was conducted with 32 healthy subjects who are native Turkish speakers. The sample was aged between 14 and 24 years. The mean age of adolescents was 16.82, whereas the young adults mean was 21.77 years. Of these participants, 37.5% were male ($n=12$), 62.5% were female ($n=20$). The recruitment procedure of the participants was followed by using the announcement network of Bilkent University and distributing flyers which advertise the study in the other educational institutions in the city of Ankara. As a precondition to participate to the experiment, the subjects were needed to have a normal visual acuity or a corrected vision since the perception of the stimuli is highly important. Prior to beginning the experiment, all the subjects (if they are under 18, their legal custodians) provided written informed consent and after completing all the steps of the experiment successfully, they were paid 50 Turkish Lira for their spent time. Exclusion criteria were any diagnosed psychiatric illness, usage of psychotic drugs or any focal anatomical abnormalities found by MRI. The study was approved by the Bilkent University Human Research Ethics Committee.

2.2 Proneness to Psychosis Assessment

The Structured Interview for Schizotypy (SIS-R) was used to examine psychosis levels of the subjects [111]. The subjects were expected to answer all the questions by themselves using a lab computer while being isolated in the lab. The SIS containing 10 sections, which investigate symptoms such as social isolation, introversion, hypersensitivity, referential thinking, suspiciousness, restricted affect, magical ideation, illusions, psychotic symptoms, and derealization, was conducted in Qualtrics which is a computing platform to collect and analyse the data. These symptoms were scored in accord with the catalogue of the questionnaire and the subjects who are above the threshold classified as prone to psychosis.

The reason why the Structured Interview for Schizotypy (SIS) was chosen as a behavioural measurement is that it provides the most comprehensive and extensive assessment to investigate the pathological nature of schizotypal symptoms, especially in a contextual way of which one could not possibly understand the purpose of a question [110]. Regarding the scoring method, the closed-response structure of the items with multiple independently scores makes this assessment into a remarkably reliable and valid measurement in the field [110].

In reference to how the scoring method was performed, all the items include a different type of likert scale pertaining to n-ary (e.g. 5-point likert scale for 3 multiple-choice, 7-point likert scale for 4 multiple-choice and 0-1 point for yes/no questions). The highest value of the scale was constantly assigned to the choices indicating the severe proneness to psychosis, while the lowest value of the scale was taken as a baseline to categorize the psychosis levels of the subjects. To epitomise, the question would be "When you are in a public place, how often do you have the feeling that other people are making insinuations about you?" (the example was taken from the referential thinking section of SIS) and the answer would be "Often, Sometimes, Seldom, Never" with the scores of 7, 5, 3, 1 respectively.

After determining the points corresponding to their answer from all the question for each participant, the lowest and highest total score (84 and 693 respectively) that one could get were calculated to categorize the classes as absent, mild, moderate, severe for the proneness to psychosis. While participants who obtained a total score below 253 were classified as "not prone to psychosis", participants who gained a total score above 300 were classified as "prone to psychosis" [112].

2.3 Analysis of Behavioural and Demographic Data

The behavioural data for the working memory task was analysed in SPSS version 19 (IBM) by using Univariate GLM to see any interaction of accuracy with gender and age depending on the proneness to psychosis. The dependent variable described whether there is a proneness to psychosis, whereas the fixed factor defined as gender differences and working memory performance while assigning age as a covariate. Additionally, one-way ANOVAs were used to look into any possible effect of proneness to psychosis on age, gender, and task performance accuracy. Statistical significance was set at $p = 0.05$.

2.4 Cognitive Paradigm

In this study, a verbal working memory task was used to stimulate targeted cognitive processes in the brain [113]. Zhang et al.[114] claims that in addition to a common working memory network, conducting different types of working memory tasks activate different brain areas. On the other hand, the paradigm used in this study has the advantage of providing the isolation of interested cognitive processes by using appropriate contrasts at the response phases. This paradigm also allowed the evaluation of the encoding and response phases independently. Tan et al. [115] have demonstrated that this particular paradigm is sensitive to

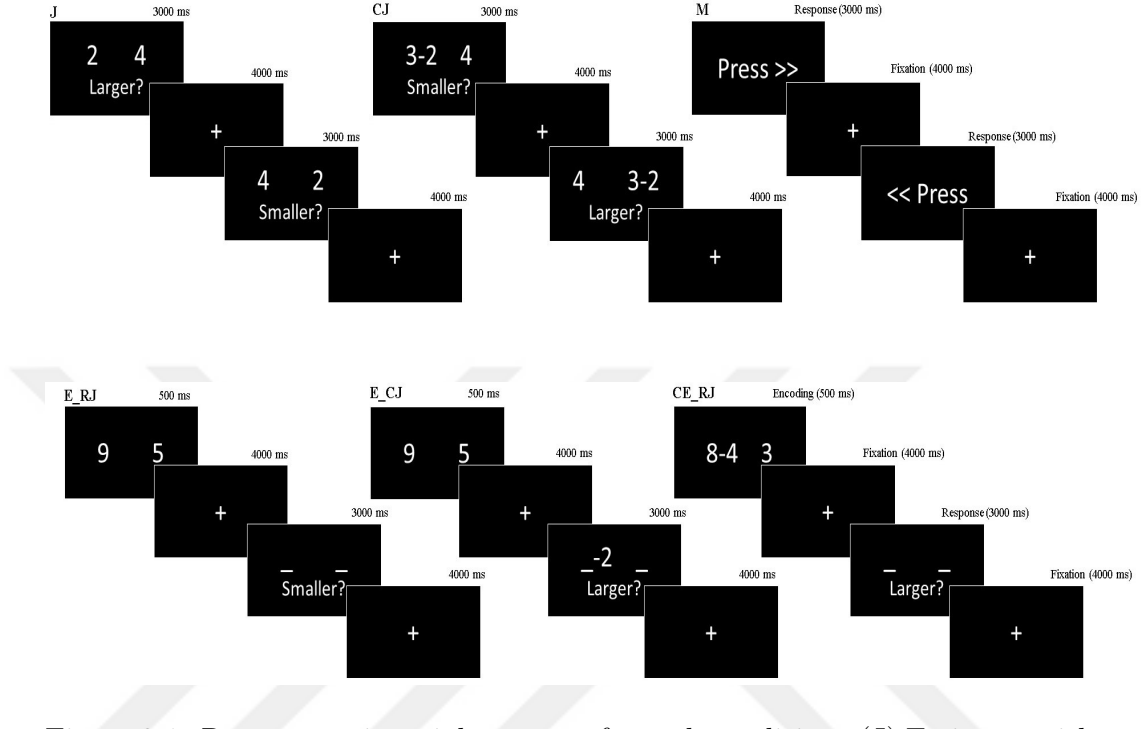


Figure 2.1: Representative trial sequence for each condition. (J) Estimate without WM. (CJ) Compute/Estimate without WM. (M) Control Task. (E_RJ) Estimate after Encoding. (E_CJ) Compute/Estimate after Encoding. (CE_RJ) Estimate after Computing during Encoding.

psychotic cognitive impairment as indicated by worse performance not only in patients but also in healthy subjects.

The working memory paradigm was designated as event-related fMRI design to avoid the predictability of the events. A brief presentation was given which explains the task and the points to take into consideration before the participants performed the task in the MRI scanner. The task was based on computationally and temporally varying information loads including five different events and a control task. Each of the events had a common response phase lasted in 3 s in which the subjects were expected to make a decision by pressing buttons either on the right side or the left side (see Fig. 2.1).

The variants of the events were as the followings: the motor task (M) where the subjects only saw a command on the screen “Press” and they were pressing the response button in which direction the arrows show; the estimate without WM

task (J) in which two digit numbers appeared on the screen and participants were asked to decide which one is larger or smaller; unlike the former one the compute/estimate without WM task (CJ) had a manipulation either on the left or right number and participants were expected to make a decision after subtraction. In the WM tasks, the only difference was they all include encoding phases (E) where two digits were first displayed on the screen and each encoding phase appeared on the screen just 0.5 s and it was followed by a 4 s fixation point. In the estimate after encoding task (E_RJ), the participants were expected to hold the information presented during the encoding phase and made their choice in the response phase based on an instruction either the larger or smaller remembered number. In the compute/estimate after encoding task (E_CJ), differently from preceding one, the subjects performed a subtraction of 2 or 3 from the retrieved number on the left or right side as stated. In the estimate after computing during the encoding task (CE_RJ), the participants were asked to compute a simple subtraction during the encoding phase and like the preceding ones they were decided their choice in the response phase. In each event, only single digits from 0 to 9 were used and the two numbers appeared on the screen left and the right side was equally balanced across 0 to 9. The difference between the numbers was no bigger than 3 and they differed by either 1 or 3 units. The manipulation was performed equally likely on the left or right number. The correct and incorrect responses also equally distributed on the left or the right side and there was an equal number of the larger or smaller instructions. All the events had 10 trials and each event was conducted depending on an order which was optimized by Wager and Nichols in 2003 [116]. But, the displayed numbers of the events on each trial were randomly generated for each subject.

2.5 MR Apparatus

The collection of MR images was performed with a 3-Tesla MRI scanner (Siemens MAGNETOM Trio) to generate high-resolution anatomical images and whole brain blood oxygen level-dependent (BOLD) functional MRI data with echo-planar imaging pulse sequence. Radio-frequency (RF) pulses were applied using

a 32-channel head coil (birdcage) to provide full brain coverage. Flexible ear protectors were used to protecting participants from the disruptive noises arising out of the nature of RF pulses generation. Head stabiliser vacuum cushions placed both sides of the head were used to meet the exclusion criteria for head movement.

Stimuli were presented via a 31.5" telemedicine LCD screen (1920 x 1080 pixel resolution and 59 Hz refresh rate) while the participants were lying on the table inside the MR scanner. A mirror was placed onto the head coil and thus the participants were able to see the screen by looking at the mirror. A stimulus delivery and experiment control program Presentation® (Neurobehavioral Systems) was used for the stimulus generation and the measurement of reaction time and accuracy for each trial. Each response given by participants during WM task was recorded through a fiberoptic response box.

2.6 MR Protocol

2.6.1 Structural MR Imaging

Before acquiring structural images, a localizer sequence which lasts for 13 seconds was performed for each participant to obtain three orthogonal slices in sagittal, coronal and transverse planes. Thereafter, the T1-weighted images were acquired with a 7 min 18 s long scan to screen anatomical structure of the brain in high resolution [176 slices, echo time, 3.02 ms; repetition time, 2.6 s; slice thickness, 1 mm; flip angle, 8°; field of view, 256 mm; matrix, 256 x 256; voxel dimensions, 1.0 x 1.0 x 1.0 mm,].

2.6.2 Functional MR Imaging

The images for functional analysis were acquired in a sequence where the participants perform working memory task in the scanner. The scans were taken 11 min 42 sec to complete the whole task and the participants were expected to make a decision in each trial. To avoid any confounding effect, the participants were in the totally dark room while they were performing the task. T2* weighted echo-planar imaging pulse sequence for acquisition of 24 contiguous slices was applied to collect whole-brain BOLD functional MRI data. The slices were acquired in an ascending interleaved pattern [echo time, 30ms; repetition time, 2 s; slice thickness, 5 mm; flip angle, 90°; field of view, 235 mm; matrix, 64 x 64, voxel dimensions, 3.7 x 3.7 x 5.0 mm]. To allow for signal saturation, the first four scans where an 8 s long fixation point appears on the screen at the beginning of the task were discarded.

2.7 Analysis of Imaging Data

2.7.1 Image Preprocessing

The anatomical and functional MRI data were stored as raw data by the software system Snygo MR B17 developed by Siemens Healthineers installed in the MR scanner computer. A software program SPM12 [117, 118, 119] (Wellcome Department of Cognitive Neurology, London, UK; <https://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab (Mathworks, Natick MA) were used to preprocess the neuroimaging data in order to use in analyses. The raw data stored as DICOM (.ima extension) files were converted to NIFTI (.nii extension) files in the batch of DICOM Import implemented in SPM to be able to process in the further steps. Converted images for each subject were realigned to the middle volume in the series and slice time corrected. Exclusion criteria for excessive movement were determined as less than 2 mm translation and less than 1.5° rotation based on literature [113, 115]. None of the subjects were excluded due to the excessive

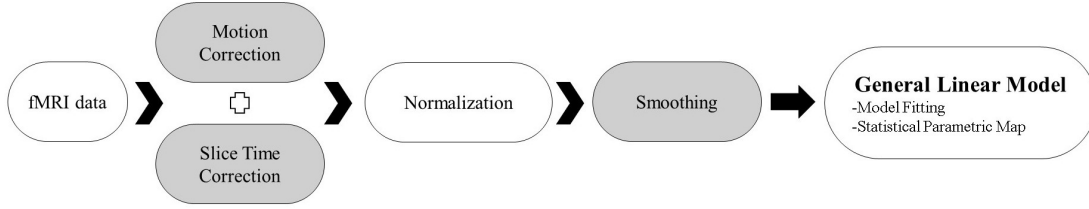


Figure 2.2: The fMRI data processing steps.

movement, they all met the criteria. After individual examination of datasets for motion, each anatomical slice were coregistered with the mean functional image as a reference. Then, a segmentation process was conducted in order to acquire deformation fields which was subsequently used in normalization step.

The low-resolution functional images were warped to high resolution anatomical images and then spatially normalized into standard stereotaxic space (Montreal Neurological Institute template) by resampling to voxel size 3.7 x 3.7 x 3.7 mm. Additionally, each subject's functional images were superimposed onto their own anatomy with 1.0 mm isometric voxels. A Gaussian filter set at 8 mm full-width at half-maximum was used for spatial smoothing of the images.

2.7.2 Statistical Analysis

The functional data which was underwent all the preprocessing steps were taken to first-level analysis for each subject. A general linear model (GLM) [120] implemented in SPM12 was used for analysing the preprocessed functional data. The responses acquired (the onsets and the accuracy) from event-related designated cognitive paradigm were modelled using the canonical hemodynamic response function. To control the systematic differences in global activity, the ratio was normalized to the whole-brain global mean. To avoid noises in the system, each individual temporally filtered using a high-pass filter of 128 s.

To isolate the BOLD activation in the brain, the cognitive subtractions were

Experimental Conditions	Cognitive Subtraction
Numerical Size Judgment	= Estimate without Working Memory - Control Task
Numerical Computation	= Compute without Working Memory - Estimate without Working Memory
Retrieval	= Estimate after Encoding - Control task
Computation in Working Memory	= Compute after Encoding - Estimate after Encoding
Integrating information within Working Memory	= Compute after Encoding - Compute without Working Memory
Computation in Encoding	= Estimate after Computing during Encoding - Estimate after Encoding

Figure 2.3: Cognitive subtraction for each contrast.

performed using the response phase onsets of each task trials. Without discrimination, the correct and incorrect responses were modelled explicitly as regressors of interest. The movement parameters derived from realignment preprocessing step were also modelled implicitly as regressors of no interests. The following contrasts were performed to infer putative cognitive processes by using the events such as M, J, CJ, E, E_RJ, E_CJ, and CE_RJ (see Fig. 2.3): numerical size judgment ($J > M$; to remove the activation of sensorimotor regions and also the visual effect of the text appeared on the screen during the task, e.g. "larger", "smaller" or "press"); numerical computation ($CJ > J$; performed to obtain simple computing activation); retrieval from WM ($E_RJ > M$; acquired only simple retrieval and also engaged as number processing); computation in WM ($E_CJ > E_RJ$; rather than rapid update of the relevant information, it also isolated integrating probe, e.g., "-2"); integrating information within WM ($E_CJ > CJ$; it reflected a comparison including the manipulation of information in WM and simple computation and beyond that temporal effect of encoded probe); computation in encoding ($CE_RJ > E_RJ$; represented the manipulation effect on temporally encoded information).

The second-level group analysis was performed to reveal arithmetic and temporal transformations of WM activation differences during the task between the

group identified as prone to psychosis and the subjects who are not prone to psychosis. To demonstrate that a statistical computation method two sample t-test was performed. The statistical matrix design as the first and second column are the no prone to psychosis subjects and the prone to psychosis subjects respectively. Additionally, age and proneness to psychosis levels were included as covariates in statistical calculation to see whether there were any significant effect on the number of activated voxels and they were defined as third and fourth columns of the designated statistical matrix respectively. The above mentioned putative cognitive subtractions was evaluated subsequently to show the main effect of each them. A threshold level of $p < 0.05$ was applied within the whole brain search volume and it was corrected for family-wise error (FWE) [121] in order to prevent false positives (alpha errors). By using Gaussian Random Field theory [122], the correlated voxels were acquired. More leniently revealed voxels $p < 0.01$ uncorrected were also reported.

Among the six contrasts mentioned above, the computation in WM and the integrating information within WM contrasts had a larger effect on prefrontal cortex as we expected. Hence, a further cluster correction analysis was applied over these contrasts at the second-level analysis in order to find significant clusters. A toolbox developed by Gaser et al. from University of Jena, threshold-free cluster enhancement (TFCE) [123] was used to generate 5000 permutations of contrasts images to test against the null distribution. The advantage which the method serves is boosting the amplitudes of spatially distributed signals without making any change on the location of their maxima while the strict control over family-wise error maintained. The resulting significant ($p < 0.05$) clusters were reported.

Chapter 3

Results

3.1 Demographic and Behavioural Results.

Regarding the behavioural performance based on accuracy level, subjects that are not prone to psychosis have a slight tendency to show more accurate performance compared to subjects that are prone to psychosis. Considering the accuracy, all the task conditions which are numerical size judgement, numerical computation, retrieval, computation in working memory, integrating information within working memory, and computation in encoding were averaged per subject to calculate the individual performance. However, this result for performance across psychosis level is not statistically significant ($F=2.75$, $p>0.05$).

Age, gender and accuracy averaged over the task conditions interaction were examined to see if any group differences exist. There were no significant psychosis level group differences in age ($F=0$, $p=0.96$), gender ($F=0.15$, $p=0.35$) and overall accuracy ($F=2.75$, $p=0.10$).

Therefore, the group differences depending on psychosis classification at the level of BOLD responses only reflected information processing physiologically, which shows no influence on the working memory performance.

	NPP	<i>s</i>	PP	<i>s</i>	<i>F</i>	<i>p</i>
	(<i>n</i> = 16)		(<i>n</i> = 16)			
Age (years)	20.12	2.93	20	2.64	0.002	0.969
Gender (number of females)	9		11		0.159	0.353
Accuracy (percentage)	0.89	0.04	0.87	0.05	2.753	0.108

(NPP: No proneness to psychosis, PP: Proneness to psychosis)

Table 3.1: The demographic and behavioural results.

3.2 Task-Related Activation

The affected regions by each cognitive subtraction were identified independently for the prone to psychosis group and the control group. The significantly altered activations in the respective contrast of interest were reported at the second-level group analysis applying the two-sample t-test (all the clusters reported could be found in Appendix B).

In the working memory tasks, the activations observed were similar for both groups and they were clustered around prefrontal cortices and parietal lobules. In the contrast correlated with computation in working memory (E_CJ>E_RJ), the significant effects for prone to psychosis subjects were observed at left pre-central gyrus (peak -44 6 34; $t=7.12$; $p<0.05$, corrected), right anterior insula (peak 41 21 -3; $t=6.59$; $p<0.05$, corrected), left middle frontal gyrus (peak -44 25 34; $t=6.47$; $p<0.05$, corrected), and left superior frontal gyrus (peak -26 -1 60; $t=4.81$; $p<0.05$, corrected) (see Fig. 3.1). When the threshold was decreased to more lenient level, larger but on the other hand weaker effects were detected at left supramarginal gyrus (peak -37 -45 41; $t=5.45$; $p<0.01$, uncorrected), right thalamus proper (peak 19 -19 0; $t=4.82$; $p<0.01$, uncorrected), right middle frontal gyrus (peak 45 29 41; $t=4.13$; $p<0.01$, uncorrected). For the control group, the activated regions different than prone to psychosis subjects were observed at left superior parietal lobule (peak -26 -64 45; $t=6.95$; $p<0.05$, corrected), right supramarginal gyrus (peak 41 -38 41; $t=6.16$; $p<0.05$, corrected), right superior parietal lobule (peak 26 -68 41; $t=6.14$; $p<0.05$, corrected), right thalamus proper (peak 11 -16 8; $t=6.04$; $p<0.05$, corrected), right anterior cingulate gyrus (peak 8 25 34; $t=5.68$; $p<0.05$, corrected) and left thalamus proper (peak -14 -16 4; $t=5.64$;

$p < 0.05$, corrected) (see Fig. 3.2). By applying Threshold Free Enhancement Method (TFCE) to avoid the strict nature of FWE correction, a small cluster at right middle frontal gyrus (peak 34 10 56; $k=16$; $p < 0.05$, corrected) was also associated with the computation in working memory task (see Appendix A).

In the contrast examining integrating information within working memory (E_CJ > CJ), weaker activations were observed compared to computation in working memory task. In the prone to psychosis subjects, at the more lenient threshold, small clusters located at left middle frontal gyrus (peak -40 3 37; $t=4.99$; $p < 0.01$, uncorrected) and right superior frontal gyrus medial segment (peak 8 40 34; $t=4.02$; $p < 0.01$, uncorrected) were observed. The only cluster acquired differently in the control group during the task was located at right superior parietal lobule (peak 15 -68 60; $t=3.02$; $p < 0.01$, uncorrected).

The significantly activated voxels related to numerical computation task (CJ > J) were observed at the right supramarginal gyrus (peak 41 -38 45; $t=5.82$; $p < 0.05$, corrected) in the control group (see Fig. 3.3). After the application of TFCE method, largely activated cluster located at the left superior parietal lobule (peak -26 -60 45; $k=121$; $p < 0.05$, corrected) and a small activated cluster found at the left precuneus (peak -7 -68 52; $k=2$; $p < 0.05$, corrected) were also detected at the end of the statistical analysis (see Appendix A). In prone to psychosis subjects, no significantly activated voxels were observed rather than small clusters distributed throughout the whole brain at the more lenient threshold ($p < 0.01$).

In the numerical size judgement task (J > M), there were no affected regions at the chosen threshold in both groups. However, when threshold was decreased to more lenient level, a small effect in the right cuneus (peak 8 -79 23; $t=4.17$; $p < 0.01$, uncorrected) was observed in prone to psychosis subjects. On the other hand, the control group had largely affected area located at left cerebellum exterior (peak -29 -68 -22; $t=5.64$; $p < 0.01$, uncorrected).

The contrast requiring computation during a brief period (0.5 s) in the encoded information (CE_RJ > E_RJ) was resulted with a weak effect on the brain in both

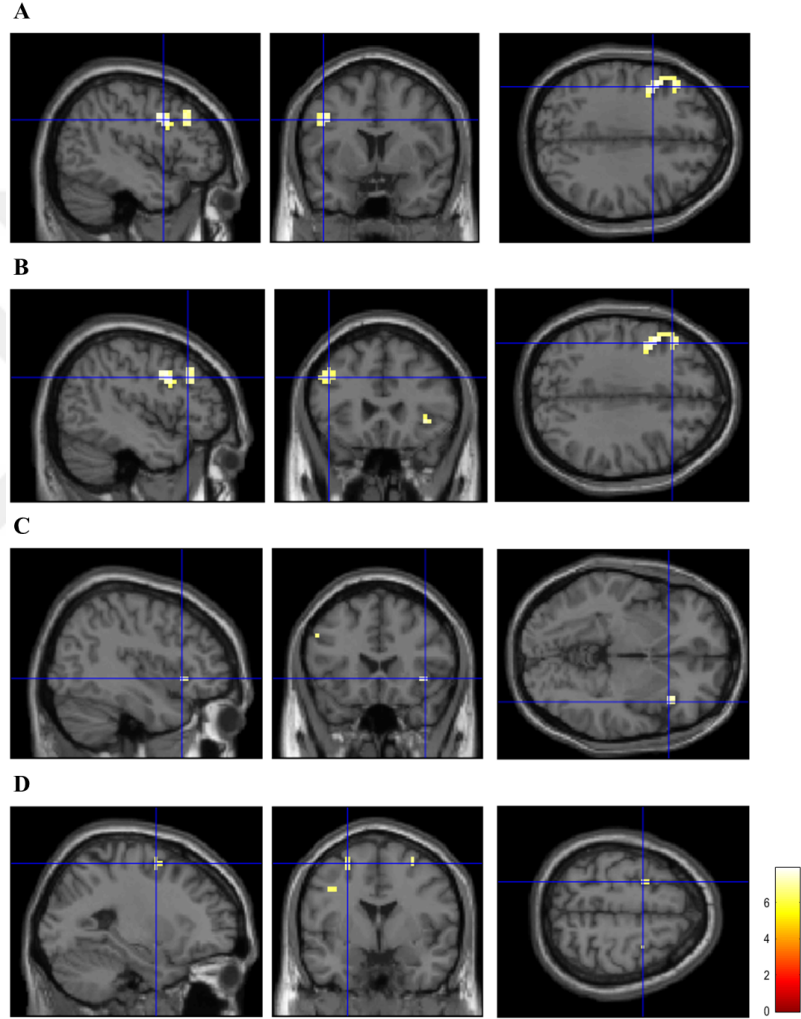


Figure 3.1: The results of computation in working memory contrast for the prone to psychosis group ($p < 0.05$, corrected): sagittal (on the left side), coronal (at the middle) and transverse (on the right side) planes are illustrated above. The activated regions are represented as (A) left precentral gyrus, (B) left middle frontal gyrus, (C) right anterior insula, (D) left superior frontal gyrus and displayed on standard stereotaxic (MNI152) space. The right hemisphere of the brain corresponds to the right side of the images.

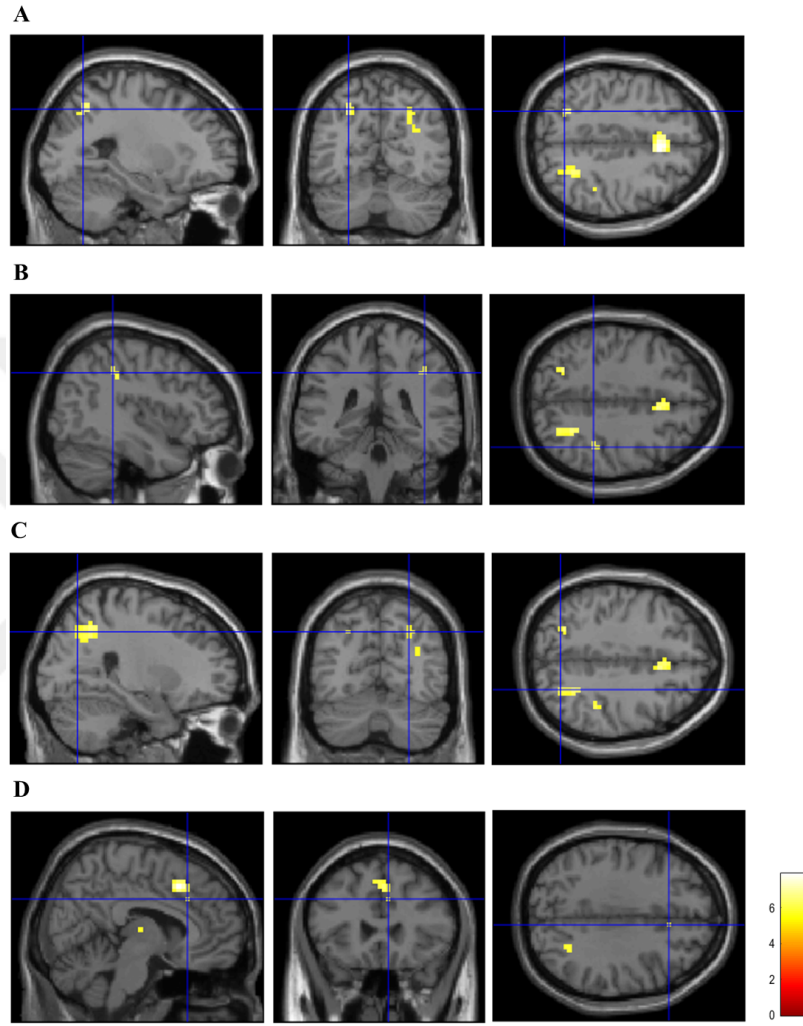


Figure 3.2: The computation in working memory contrast results for the control group ($p < 0.05$, corrected). The activated regions are represented as (A) left superior parietal lobule, (B) right supramarginal gyrus, (C) right superior parietal lobule, (D) right anterior cingulate gyrus.

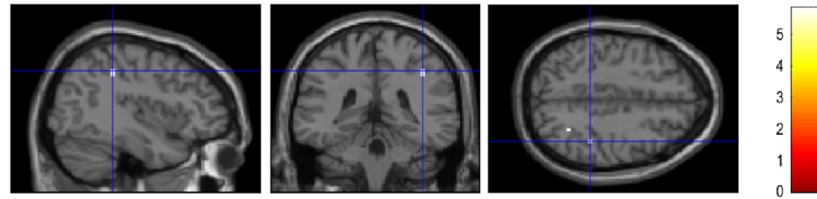


Figure 3.3: The numerical computation contrast results for the control group ($p < 0.05$, corrected).

A

Region	Coordinates	k	t
<i>Computation in Working Memory</i>			
L precentral gyrus	-44 6 34	188*	7.12
R anterior insula	41 21 -3	5	6.59
L middle frontal gyrus	-44 25 34	47	6.47
L supramarginal gyrus	-37 -45 41	691	5.45
R middle frontal gyrus	34 62 8	39	5.44
R Thalamus Proper	19 -19 0	286	4.82
L superior frontal gyrus	-26 -1 60	35*	4.81
R middle frontal gyrus	45 29 41	197	4.13
L middle frontal gyrus	-40 47 0	97	4.03
R Cerebellum Exterior	11 -75 -22	52	3.74
L occipital fusiform gyrus	-22 -79 -7	77	3.56
L Cerebellum Exterior	-37 -64 -33	15	3.34
R supplementary motor cortex	8 10 56	182*	

B

Region	Coordinates	k	t
<i>Computation in Working Memory</i>			
L superior parietal lobule	-26 -64 45	67*	6.95
R supramarginal gyrus	41 -38 41	6	6.16
R superior parietal lobule	26 -68 41	344*	6.14
R Thalamus Proper	11 -16 8	2	6.04
R anterior cingulate gyrus	8 25 34	1214*	5.68
L Thalamus Proper	-14 -16 4	1	5.64
L Cerebellum Exterior	-14 -49 -18	15	2.86
R Cerebellum Exterior	26 -64 -26	66*	
Brain Stem	8 -27 -7	18*	
R middle frontal gyrus	34 10 56	16*	
L supramarginal gyrus	-44 -42 41	2*	

Table 3.2: The activated regions during the computation in working memory task. While Table A represents the activated regions for prone to psychosis group, Table B lists the activated regions for the control group. The columns represent the regions activated, the coordinates, the number of voxels (k) and t values respectively from left to right. The rows marked as bold show the activated regions at the threshold $p < 0.05$ corrected, the rest of the rows are thresholded at $p < 0.01$ uncorrected. The asterisk represents the clusters in which the TFCE method applied.

A

Region	Coordinates	k	t
<i>Numerical Computation</i>			
R Thalamus Proper	23 -23 0	71	4.74
L middle occipital gyrus	-29 -93 8	119	3.95
R frontal operculum	45 21 -3	46	3.65
R supplementary motor cortex	4 6 60	33	3.61
R superior occipital gyrus	30 -79 30	20	3.60
R middle frontal gyrus	34 3 60	17	3.49
L Cerebellum Exterior	-3 -56 -40	17	3.48
R middle frontal gyrus	45 43 26	12	2.98

B

Region	Coordinates	k	t
<i>Numerical Computation</i>			
R supramarginal gyrus	41 -38 45	151*	5.82
L supplementary motor cortex	-3 18 41	293	4.58
L orbital part of the inferior frontal gyrus	-33 25 -7	506	4.54
Brain Stem	-7 -27 -7	22	4.40
R anterior insula	30 25 -7	76	4.26
R Thalamus Proper	11 -8 4	109	4.11
R middle frontal gyrus	41 43 15	87	3.91
L middle temporal gyrus	-48 -38 0	49	3.44
L superior parietal lobule	-26 -60 45	121*	
R Cerebellum Exterior	8 -75 -18	16*	
L Cerebellum Exterior	-14 -86 -22	3*	
L precuneus	-7 -68 52	2*	

Table 3.3: The activated regions during the numerical computation contrast: (A) The prone to psychosis group, (B) The control group.

groups. While the left middle frontal gyrus (peak -44 47 -3; $t=4.61$; $p<0.01$, uncorrected) was activated weakly in prone to psychosis subjects, the activation located at the right superior parietal lobule (peak 26 -64 41; $t=3.08$; $p<0.01$, uncorrected) was observed in the control group.

At the retrieval task (E_RJ>M), no effect was observed rather than a small fraction at the left middle cingulate gyrus (peak 0 21 30; $t=3.46$; $p<0.01$, uncorrected) in the prone to psychosis subjects and small clusters located at bilateral cerebellum exterior (for the left hemisphere; peak -7 -68 -18; $t=3.12$; $p<0.01$, uncorrected; for the right hemisphere; peak 19 -60 -22; $t=2.83$; $p<0.01$, uncorrected) in the control group.

3.3 Proneness to Psychosis Effects in Cognitive Processes of Interest

A second-level group analysis where inter-subject variability treated as a random effect was performed by applying the two-sample t-test to demonstrate the significant difference between the two groups. Each contrast identified above were examined to detect any altered activation due to the proneness to psychosis. Besides that in order to demonstrate whether any positive or negative correlation, the ages and psychosis levels of the participants were used as covariates in the analysis.

At the chosen threshold ($p>0.05$, corrected), there were no altered activation due to proneness to psychosis. On the other hand, when the threshold was decreased to more lenient level ($p>0.01$, uncorrected), the slightly altered activation for every contrast except the computation in encoding (CE_RJ>E_RJ) was observed (see Table 3.4). In the cognitive process of computation in working memory (E_CJ>E_RJ), an increased activation at left middle frontal gyrus (peak -44 29 41; $t=3.43$; $p<0.01$, uncorrected) was observed (see Fig. 3.4). On the other hand, the integrating information in working memory task (E_CJ>CJ) had

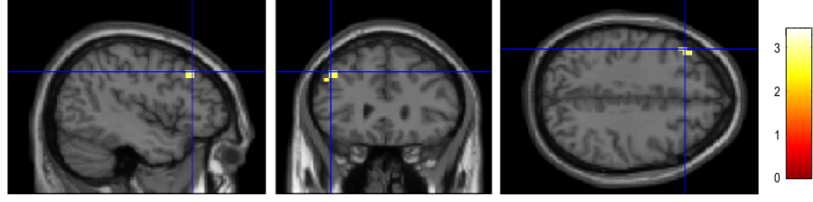


Figure 3.4: The increased activation due to proneness to psychosis for the computation in working memory contrast result (PP>NPP).

three increased activation regions located at the left middle frontal gyrus (peak -40 3 37; $t=3.45$; $p<0.01$, uncorrected), the right superior frontal gyrus (peak 19 40 52; $t=2.86$; $p<0.01$, uncorrected) and the left superior temporal gyrus (peak -55 -34 4; $t=2.68$; $p<0.01$, uncorrected) (see Fig. 3.5). Besides those, the right supramarginal gyrus (peak 60 -23 37; $t=2.74$; $p<0.01$, uncorrected) showed a tendency to decrease in activation for prone to psychosis subjects (see Fig. 3.6).

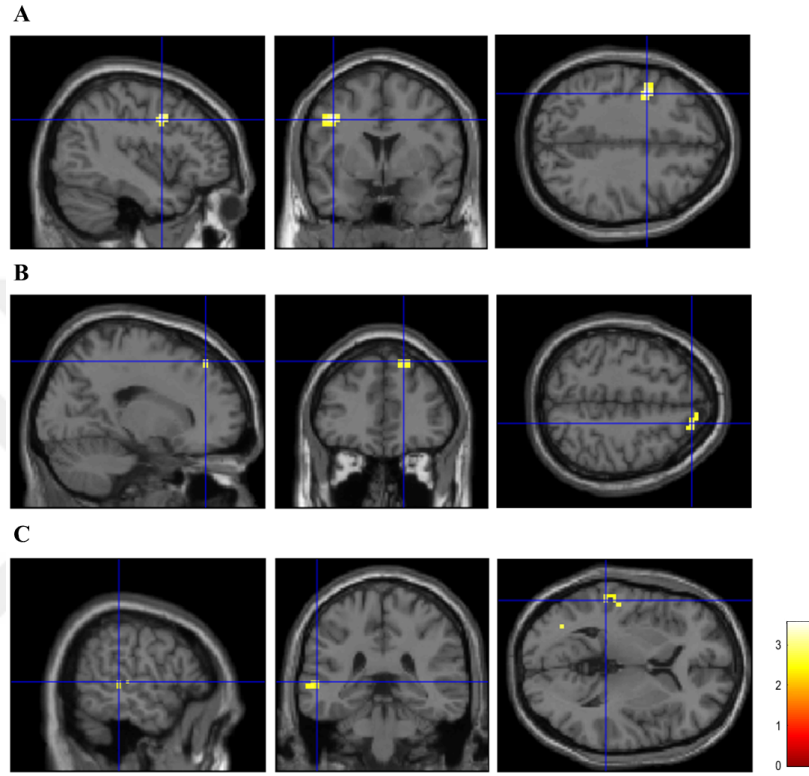


Figure 3.5: The increased activation due to proneness to psychosis for the integrating information in working memory contrast result (PP>NPP). The regions illustrated above were (A) left middle frontal gyrus, (B) right superior frontal gyrus (C) left superior temporal gyrus.

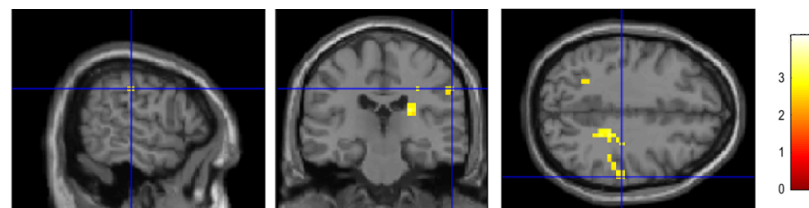


Figure 3.6: The decreased activation due to proneness to psychosis for the integrating information in working memory contrast result (NPP>PP).

A			
Region	Coordinates	k	t
<u>Numerical Size Judgment</u>			
No voxels survived			
<u>Numerical Computation</u>			
No voxels survived			
<u>Retrieval</u>			
R postcentral gyrus medial segment	8 -27 48	12	2.99
<u>Computation in Working Memory</u>			
L middle frontal gyrus	-44 29 41	11	3.43
<u>Integrating Information in Working Memory</u>			
L middle frontal gyrus	-40 3 37	18	3.45
R superior frontal gyrus	19 40 52	10	2.86
L superior temporal gyrus	-55 -34 4	10	2.68
<u>Computation in Encoding</u>			
No voxels survived			
B			
Region	Coordinates	k	t
<u>Numerical Size Judgment</u>			
R superior temporal gyrus	56 -8 -11	87	4.35
L Cerebellum Exterior	-29 -68 -22	42	3.74
R middle frontal gyrus	37 10 56	17	3.34
R lingual gyrus	26 -49 -7	27	2.80
L middle frontal gyrus	-37 51 15	10	2.70
L middle cingulate gyrus	-3 -1 30	11	2.60
<u>Numerical Computation</u>			
L superior temporal gyrus	-48 -34 0	28	3.30
<u>Retrieval</u>			
R Cerebellum Exterior	11 -75 -22	13	3.04
<u>Computation in Working Memory</u>			
No voxels survived			
<u>Integrating Information in Working Memory</u>			
R supramarginal gyrus	60 -23 37	14	2.74
<u>Computation in Encoding</u>			
No voxels survived			

Table 3.4: The regions which had altered activations during each contrast. (A) The prone to psychosis group>The control group, (B) The control group>The prone to psychosis group.

Chapter 4

General Discussion and Conclusion

The primary objective of this thesis was to present evidence that the subjects mildly prone to psychosis have altered brain activations in a well-established verbal WM task in which consist of computationally and temporally varying information loads. Even though, there are studies on the subjects who are at the high-risk level of psychosis in the literature [124], the effect of mild proneness to psychosis in WM impairment has not been examined before in the literature to our knowledge. The task-related activation results in our study may interpreted as computation and integrating requiring processes in the brain are weakly altered due to mild proneness to psychosis. It is needed to be underlined that under the strict conditions of FWE analysis, these alterations has not been observed. Nevertheless, the WM impairment in prone to psychosis is a progressive symptom as demonstrated in the subjects varying from healthy controls to first episode psychosis patients [98], thus our results could be claimed as consistent with the literature. According to our findings, computation requiring processes have a stronger influence on specific regions located in prefrontal and parietal cortices compared to numerical computation without WM in both groups. However, the effect of mild proneness to psychosis has caused to a weak alteration on a specific region which is the middle frontal gyrus. The integrating information of WM

processes have not shown a strong effect in both groups, on the other hand, the mild proneness to psychosis have exhibited weak alterations but a larger effect on the prefrontal cortex (e.g. left middle frontal gyrus and right superior frontal gyrus). The alterations have also observed in the left superior temporal gyrus and the right supramarginal gyrus which are out of the PFC. These findings suggest that while the computation requiring information processes in WM is disrupted in a specific pattern which affects the frontal lobe, the integration of information processes in WM is altered the activation in a larger network in the brain due to mild proneness to psychosis.

Age-associated developmental transformations are considered as an important factor which influence the progress of working memory deficits [124, 125]. Previous works conducted on age-related WM activations have concluded with the idea that in regions where the activation increased (e.g. higher order cortices) are performance enhancing regions, whereas decreased network activation is interpreted as a circuitry needed to be pruned during the developmental period of adolescent [78, 126]. In our study, the influence of ageing was investigated as a covariate in the statistical analysis of functional images. The age-association has not shown any significant effect on each contrast. This inconsistency with the literature may have emerged from our sample size. A strong statistical power requires a meaningful sample size for each age group and we were not able to assess enough number of subjects (e.g. age of 15) for each group. Additionally, we have used the proneness to psychosis score in SIS-R as a covariate as well and investigated that whether the WM activation would be altered directly or inversely proportional to the proneness scores. However, the effect of the proneness scores have not affected the activation level of WM processes in a significant manner.

One of the most commonly investigated factor in the psychopathology of psychosis is the gender differences. Nevertheless, many of these studies considering the first episode psychosis or at risk mental state individuals resulted with inconsistency. In a study which specifically focused on the gender differences in psychosis has demonstrated that the gender difference is not an effective factor among neither in at high-risk mental state or first episode psychosis group

[127]. The only difference was while the female subjects had higher scores in the positive symptom assessments, the male subjects had higher scores in negative symptom assessments. In the behavioural results of our study, we have not observed any significant correlation between gender differences and proneness to psychosis scores in parallel with the study of Gonzalez et al.

Additionally, the working memory deficiency is a well-described cognitive impairment in first episode psychosis and ultra high risk individuals [128]. The subjects who developed later on psychosis are shown poorer performance in working memory tests [61]. The working memory accuracy between the prone to psychosis group and the control group did not differ significantly compared to their psychosis scores in SIS-R. Even though we have observed greater difference compared to other factors in the behavioural analysis, there was no meaningful correlation.

In this study, we have used a very well-established proneness to psychosis assessment (SIS-R) in order to classify the mildly prone group and the subjects for control. The subjects who diagnosed with psychiatric illnesses or using psychiatric drugs were excluded. The working memory task used was a well-designated paradigm to stimulate the network associated with working memory activation and to detect alterations related to proneness to psychosis. Each individual was analysed separately to prevent the performance differences among the subjects and the whole brain was examined applying the strict voxelwise correction to acquire the most powerful statistical results. While these features represent the strengths of our study and there were the weak sides which have to be emphasized at the same time. Firstly, the sample size for both group was small to obtain a stringent statistical analysis. A larger sample pool would lead to more meaningful results. We have also performed a cross-sectional analysis to observe the alterations in the brain due to proneness to psychosis. The development of the same subjects should be followed, and a within-subject analysis performed to observe change over time.

The future aspect of this study is determining the developmental trajectories of the working memory. In order to achieve this, the brain development of the subjects should be followed by performing the same experiment one year later.

Thus, a within-subject would be able to be performed to test the change over time. With the collection of blood or saliva samples, the polygenic risk scores and miRNA profiling of each subject could be generated, and this will allow to investigate the reciprocal causation models for the psychosis. Due to the fact that our subjects are healthy volunteers, an *in silico* analysis would be appropriate to compare the profiles of our subjects and the psychotic patients.

Moreover, a widely used approach in the analysis of fMRI data is the regions of interest (or ROI) analysis in which the signals are extracted from a specified region [129]. The ROI analysis is often useful for the designs which have multiple levels. By plotting each condition and comparing against other variables of interest, the signal of the interested region becomes discernible. Another advantage which ROI analysis serves is controlling the Type I error by limiting the number of statistical tests to a few ROIs [129]. In a previous study where working memory performance investigated, the left DLPFC was chosen as a region of interest in order to avoid the type I error [130]. Furthermore, in the study of Tan et al. [113], an additional functional ROI analysis was conducted to isolate the signal more distinguishable around the prefrontal cortex, posterior parietal cortex and striatum. As an additional future aspect for this study, an ROI can be determined based on the results of the study (e.g. middle frontal gyrus). A functional ROI could not be appropriate because, when the activation signal is not strong, the signals acquired could be very noisy. Alternatively, estimating the region of interest using the anatomical images would be more convenient.

Another future aspect of this study might be conducting an effective connectivity analysis to reveal the correlation between impaired regions due to proneness to psychosis and the strongly activated intact regions. While functional connectivity refers to the simple temporal correlation between activation of spatially segregated neural events, the effective connectivity based on a mathematical model which reveals that how one neuronal system is influential over another [131]. In a study which investigates the causal relationships between cortical-cortical and cortical-subcortical networks selectively engaged during maintenance and manipulation operations in working memory has been used dynamic causal

modelling (DCM) [132] to demonstrate correlations between the associated networks [115]. Another study has been conducted a psychophysiological interaction analysis (PPI) [133] to test whether patients show a de-coupling of regions that are functionally connected during WM demands (e.g. DLPFC with parietal regions) [125]. On the other hand, both of the methods require a strongly activated seed region to demonstrate the correlation with regions. When the sample size could be enlarged in the future, both methods are capable of to demonstrate the impairment of working memory network caused by the proneness to psychosis.

As a conclusion, we have used proneness to psychosis as a measure of network signalling alteration in healthy human volunteers to investigate transformation of working memory. Manipulating and rapid updating of information processes are involved in a larger network of prefrontal cortex and superior parietal lobule. This study suggests that the mild proneness to psychosis has a weak effect on the working memory processes and that specific alterations in the prefrontal and parietal lobules may be associated with the onset of psychosis.

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Appendix A

Figures



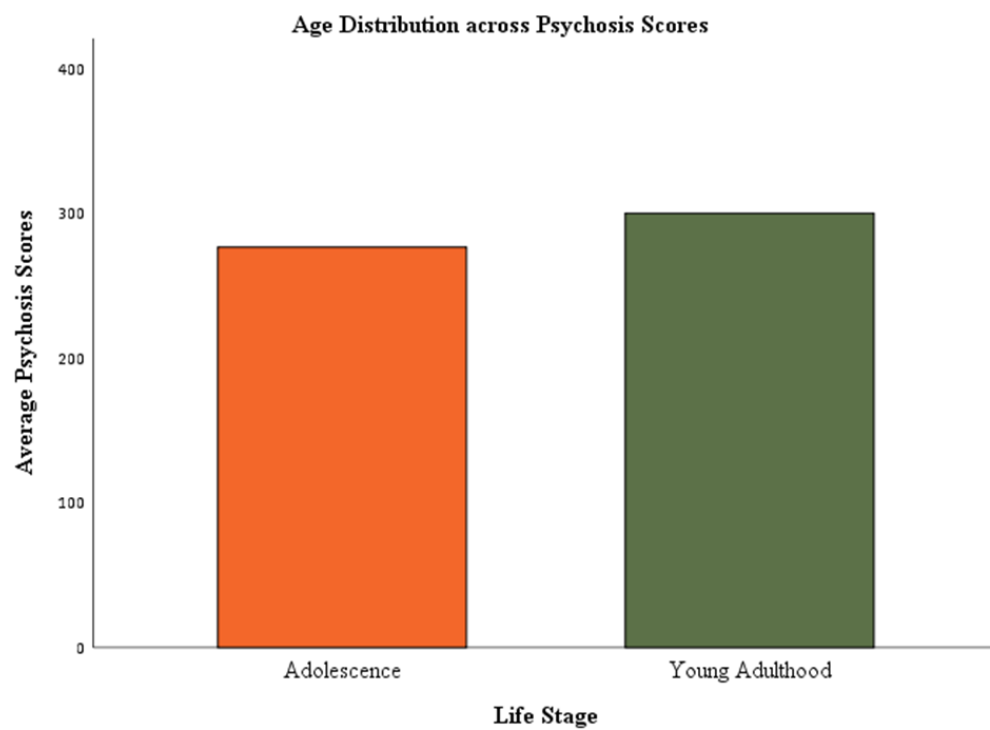


Figure A.1: The comparison of average psychosis scores between adolescent subjects and young adult subjects. The adolescence group consists of the subjects who are at the age of 14-19 and the young adult group consists of the subjects who are at age of 20-24.

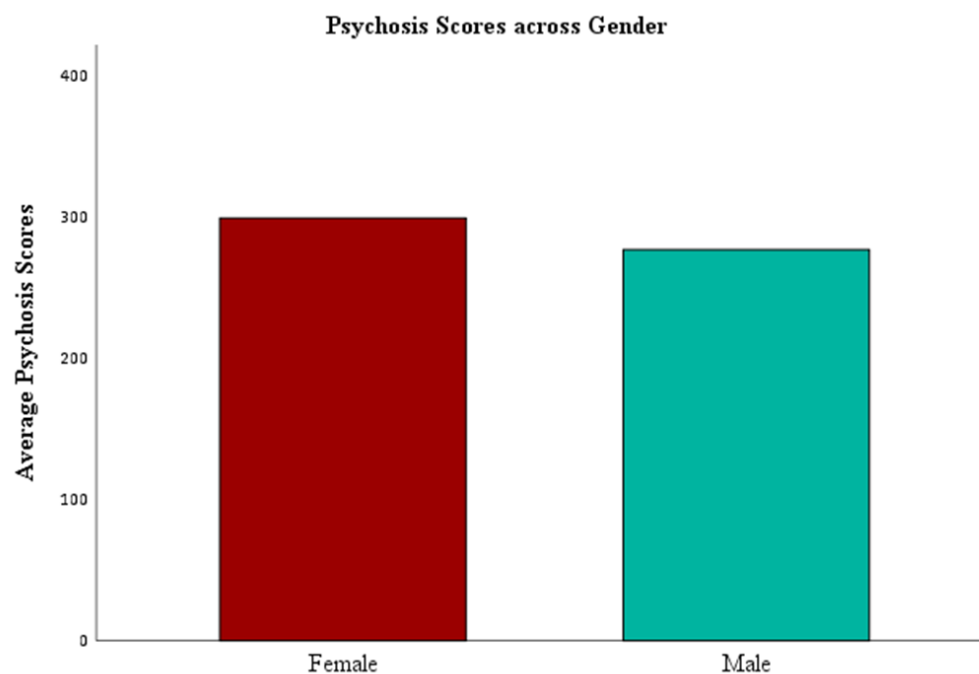


Figure A.2: The comparison of average psychosis across gender.

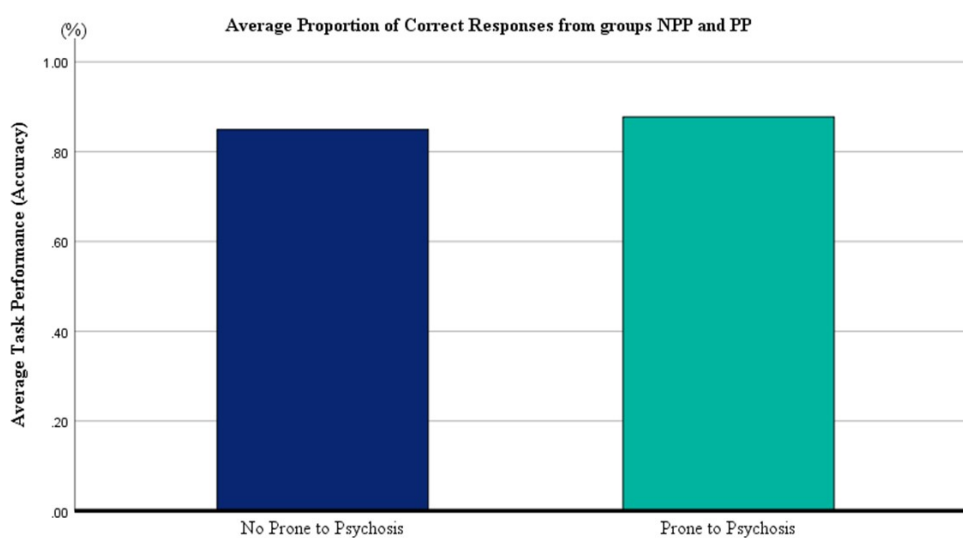
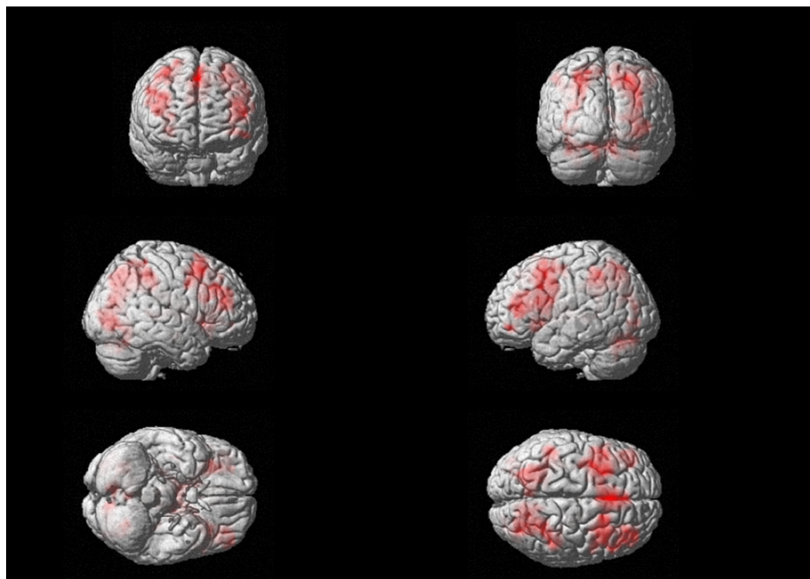


Figure A.3: The comparison of average task performance rates between the prone to psychosis group and the control group.

A



B

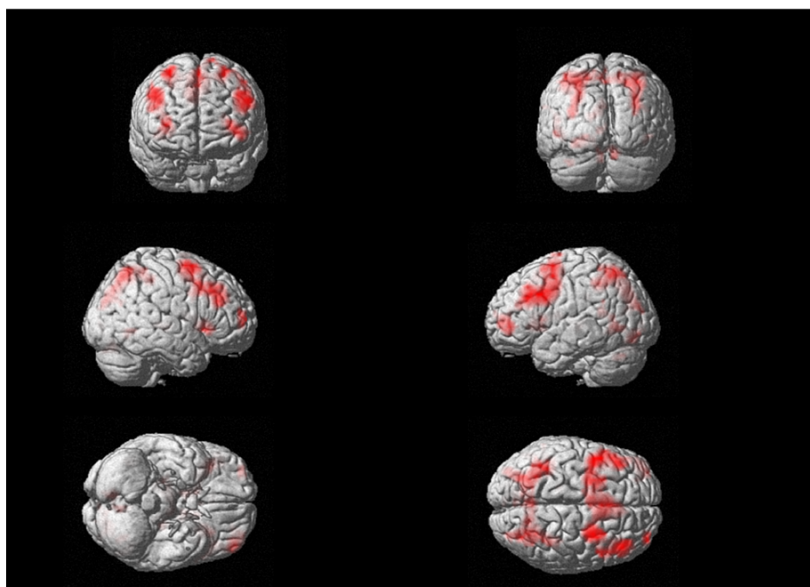


Figure A.4: The whole brain illustration of activated regions observed in the computation in working memory contrast for both groups. The threshold was determined as $p < 0.01$, uncorrected.

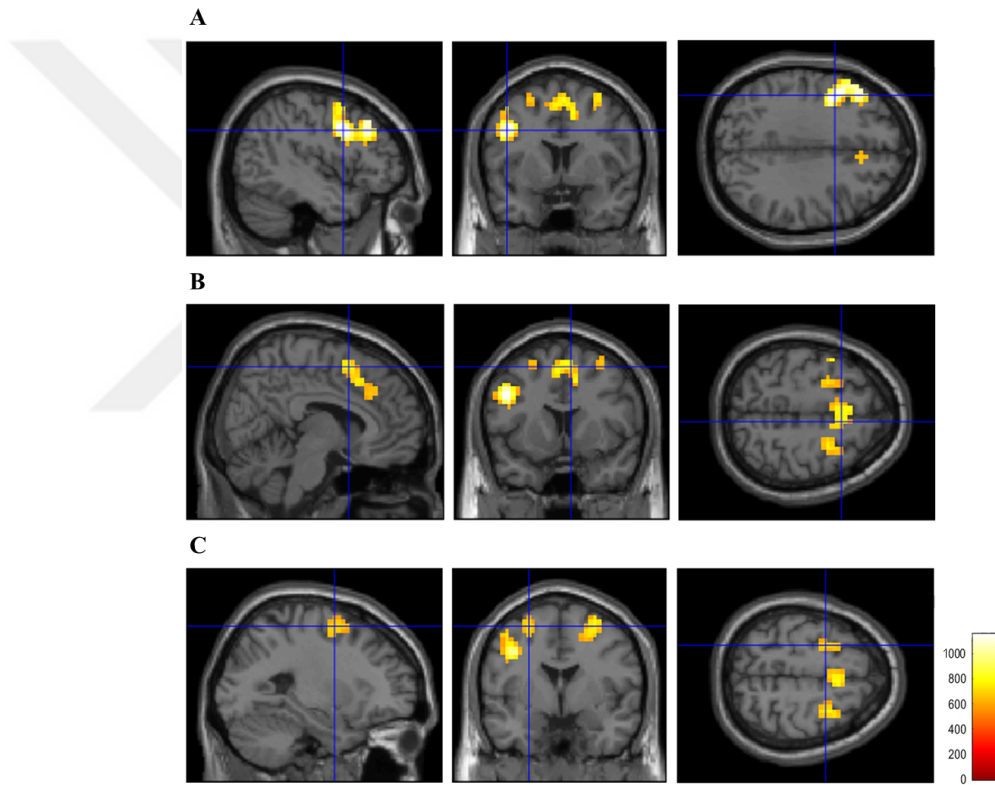


Figure A.5: The clusters observed by applying TFCE method for computation in working memory contrast in the prone to psychosis group. The activated regions are represented as (A) left precentral gyrus, (B) left supplementary motor cortex, (C) left superior frontal gyrus and displayed on standard stereotaxic (MNI152) space.

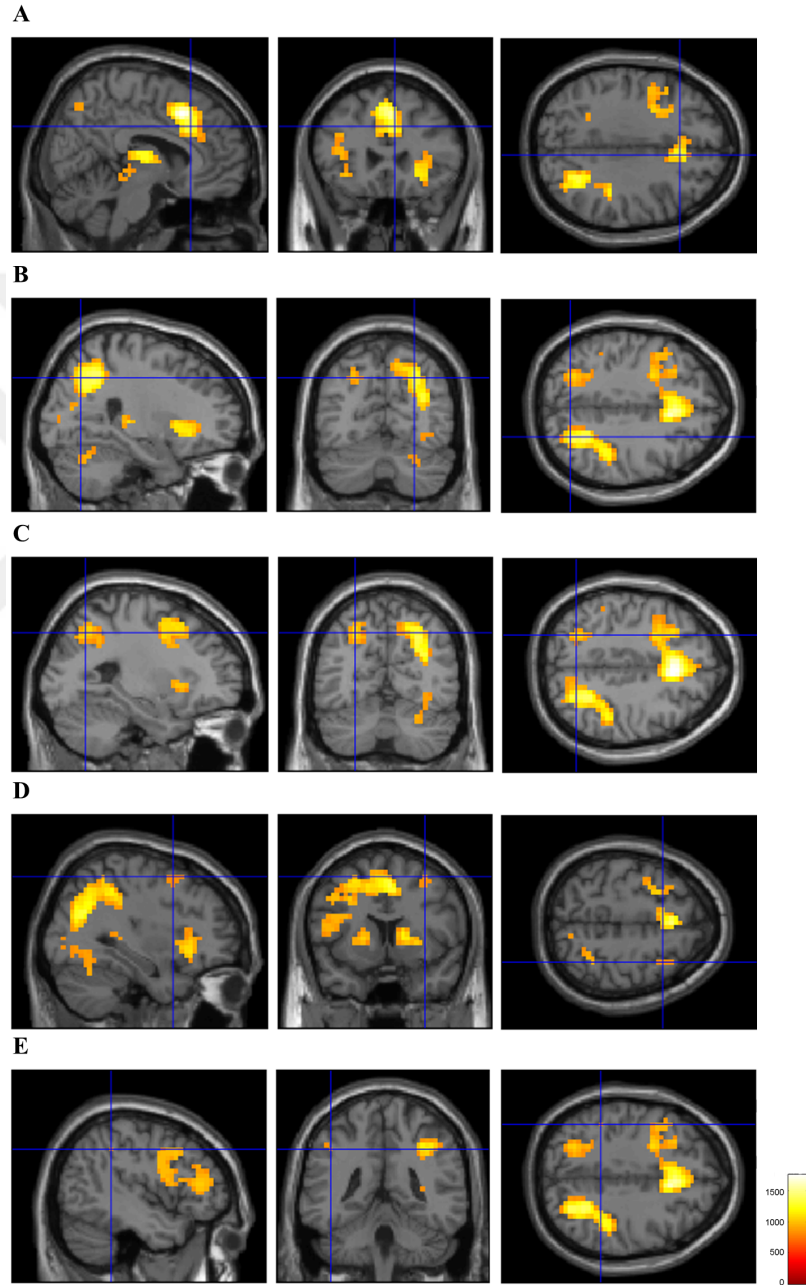


Figure A.6: The clusters observed by applying TFCE method for computation in working memory contrast in the control group: (A) right anterior cingulate gyrus, (B) right superior parietal lobule, (C) left superior parietal lobule, (D) right middle frontal gyrus, (E) left supramarginal gyrus.

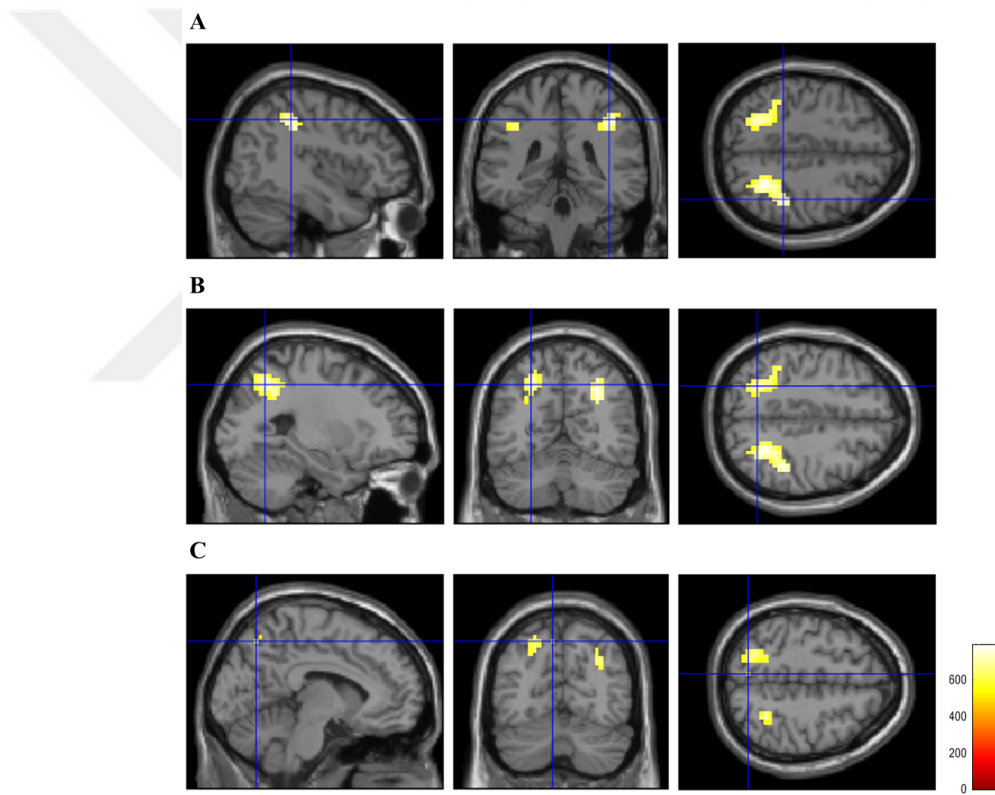


Figure A.7: The clusters observed by applying TFCE method for numerical computation contrast in the control group: (A) right supramarginal gyrus, (B) left superior parietal lobule, (C) left precuneus.

Appendix B

Tables



Proneness to Psychosis (≥ 300)														
Subject No	ID	Age	Gender	Social Isolation	Introversion	Hypersensitivity	Referential Thinking	Suspiciousness	Restricted Affect	Magical Ideation	Illusions	Psychotic symptoms	Derealisation/Depersonalization	Total
Subject 1	1101	24	M	19	17	31	84	80	14	54	44	10	3	356
Subject 2	1105	20	M	22	11	43	94	89	6	54	43	32	21	415
Subject 3	2105	20	F	22	15	39	43	68	14	60	35	7	11	314
Subject 4	1110	16	F	29	18	33	98	73	14	70	48	18	21	422
Subject 5	2110	16	F	15	20	41	88	85	12	60	44	18	21	404
Subject 6	1113	21	F	25	11	35	106	64	6	50	68	42	15	422
Subject 7	2113	21	F	26	11	29	93	54	8	36	35	36	9	337
Subject 8	2114	23	F	21	17	27	116	103	18	60	64	32	21	479
Subject 9	3115	23	F	29	22	31	77	79	16	16	30	14	7	321
Subject 10	2119	17	F	33	26	33	96	69	18	82	66	19	11	453
Subject 11	1119	17	F	21	13	41	93	73	8	60	53	24	9	395
Subject 12	1125	17	M	17	16	29	72	63	6	60	24	36	9	332
Subject 13	2126	21	M	16	13	25	106	77	12	74	54	45	13	435
Subject 14	2129	20	F	21	12	41	87	59	8	28	34	33	7	330
Subject 15	2133	20	F	25	21	25	75	87	22	44	32	27	19	377
Subject 16	1134	24	M	19	19	25	57	70	16	52	32	25	3	318

No Proneness to Psychosis (< 253)														
Subject No	ID	Age	Gender	Social Isolation	Introversion	Hypersensitivity	Referential Thinking	Suspiciousness	Restricted Affect	Magical Ideation	Illusions	Psychotic symptoms	Derealisation/Depersonalization	Total
Subject 17	2100	22	M	18	9	21	12	62	12	34	15	15	3	201
Subject 18	2101	24	M	19	15	12	38	70	20	34	21	13	3	245
Subject 19	2102	19	M	19	26	23	31	48	22	16	27	10	3	225
Subject 20	1103	19	F	19	8	23	23	38	8	32	12	8	3	174
Subject 21	2104	14	F	19	10	17	37	43	6	18	15	8	3	176
Subject 22	1104	14	F	24	12	23	50	51	8	28	21	13	3	233
Subject 23	1106	23	F	22	10	23	53	31	6	30	29	12	9	225
Subject 24	1115	23	F	20	9	29	39	42	12	18	25	16	10	220
Subject 25	1117	23	M	23	11	23	29	48	14	26	32	13	3	222
Subject 26	2121	22	F	24	10	29	40	41	6	38	28	18	9	243
Subject 27	1122	22	F	22	10	29	12	42	8	38	20	12	3	196
Subject 28	1123	18	M	21	14	11	18	49	12	20	27	13	5	190
Subject 29	2123	18	M	23	9	19	33	39	12	16	17	6	3	177
Subject 30	1128	20	M	30	17	9	34	31	22	16	21	13	3	196
Subject 31	1130	21	F	17	12	27	46	49	10	22	20	21	3	227
Subject 32	2131	20	F	24	17	21	48	41	16	36	13	11	5	232

Table B.1: The table represents the scores of each symptom measured in the proneness to psychosis assessment (SIS-R) for each subject.

Region	Coordinates	k	t
<i>Numerical Size Judgment</i>			
R Cuneus	8 -79 23	171	4.17
Brain Stem	4 -42 -44	11	3.20
R occipital fusiform gyrus	26 -71 -7	18	3.12
<i>Numerical Computation</i>			
R Thalamus Proper	23 -23 0	71	4.74
L middle occipital gyrus	-29 -93 8	119	3.95
R frontal operculum	45 21 -3	46	3.65
R supplementary motor cortex	4 6 60	33	3.61
R superior occipital gyrus	30 -79 30	20	3.60
R middle frontal gyrus	34 3 60	17	3.49
L Cerebellum Exterior	-3 -56 -40	17	3.48
R middle frontal gyrus	45 43 26	12	2.98
<i>Retrieval</i>			
L middle cingulate gyrus	0 21 30	19	3.46
<i>Computation in Working Memory</i>			
L precentral gyrus	-44 6 34	188*	7.12
R anterior insula	41 21 -3	5	6.59
L middle frontal gyrus	-44 25 34	47	6.47
L supramarginal gyrus	-37 -45 41	691	5.45
R middle frontal gyrus	34 62 8	39	5.44
R Thalamus Proper	19 -19 0	286	4.82
L superior frontal gyrus	-26 -1 60	35*	4.81
R middle frontal gyrus	45 29 41	197	4.13
L middle frontal gyrus	-40 47 0	97	4.03
R Cerebellum Exterior	11 -75 -22	52	3.74
L occipital fusiform gyrus	-22 -79 -7	77	3.56
L Cerebellum Exterior	-37 -64 -33	15	3.34
R supplementary motor cortex	8 10 56	182*	
<i>Integrating Information in Working Memory</i>			
L middle frontal gyrus	-40 3 37	171	4.99
L middle frontal gyrus	-37 55 0	109	4.61
R superior frontal gyrus medial segment	8 40 34	87	4.02
R middle frontal gyrus	37 58 8	24	3.50
L superior frontal gyrus	-26 -5 60	31	3.46
L middle temporal gyrus	-59 -34 0	19	3.26
R middle frontal gyrus	45 32 30	13	2.94
<i>Computation in Encoding</i>			
L middle frontal gyrus	-44 47 -3	92	4.61
L middle frontal gyrus	-48 25 34	89	3.57
R transverse temporal gyrus	41 -27 15	11	3.19
L superior frontal gyrus	-26 3 67	15	3.33
R middle frontal gyrus	34 58 11	23	3.14
L angular gyrus	-40 -60 56	36	3.12

Table B.2: The clusters observed for each contrast in the prone to psychosis group. The columns represent the regions activated, the coordinates, the number of voxels (k) and t values respectively from left to right. The rows marked as bold show the activated regions at the threshold $p < 0.05$ corrected, the rest of the rows are thresholded at $p < 0.01$ uncorrected. The asterisk represents the clusters in which the TFCE method applied.

Region	Coordinates	k	t
<i>Numerical Size Judgment</i>			
L Cerebellum Exterior	-29 -68 -22	1053	5.64
L supplementary motor cortex	-3 6 56	98	4.20
R superior occipital gyrus	23 -82 23	35	3.53
R precentral gyrus	41 -1 60	74	3.30
L middle cingulate gyrus	-3 -27 37	21	3.10
L precentral gyrus	-44 -8 60	13	3.09
<i>Numerical Computation</i>			
R supramarginal gyrus	41 -38 45	151*	5.82
L supplementary motor cortex	-3 18 41	293	4.58
L orbital part of the inferior frontal gyrus	-33 25 -7	506	4.54
Brain Stem	-7 -27 -7	22	4.40
R anterior insula	30 25 -7	76	4.26
R Thalamus Proper	11 -8 4	109	4.11
R middle frontal gyrus	41 43 15	87	3.91
L middle temporal gyrus	-48 -38 0	49	3.44
L superior parietal lobule	-26 -60 45	121*	
R Cerebellum Exterior	8 -75 -18	16*	
L Cerebellum Exterior	-14 -86 -22	3*	
L precuneus	-7 -68 52	2*	
<i>Retrieval</i>			
L Cerebellum Exterior	-7 -68 -18	23	3.12
R Cerebellum Exterior	19 -60 -22	22	2.83
<i>Computation in Working Memory</i>			
L superior parietal lobule	-26 -64 45	67*	6.95
R supramarginal gyrus	41 -38 41	6	6.16
R superior parietal lobule	26 -68 41	344*	6.14
R Thalamus Proper	11 -16 8	2	6.04
R anterior cingulate gyrus	8 25 34	1214*	5.68
L Thalamus Proper	-14 -16 4	1	5.64
L Cerebellum Exterior	-14 -49 -18	15	2.86
R Cerebellum Exterior	26 -64 -26	66*	
Brain Stem	8 -27 -7	18*	
R middle frontal gyrus	34 10 56	16*	
L supramarginal gyrus	-44 -42 41	2*	
<i>Integrating Information in Working Memory</i>			
R superior parietal lobule	15 -68 60	11	3.02
<i>Computation in Encoding</i>			
R superior parietal lobule	26 -64 41	57	3.08
R Pallidum	26 -12 -3	10	3.04

Table B.3: The clusters observed for each contrast in the control group.