Aus der Klinik für Psychiatrie und Psychotherapie

des Fachbereichs Medizin der Philipps-Universität Marburg

Direktor: Prof. Dr. Tilo Kircher

# Brain activation during a working memory task in schizophrenia and major depression

INAUGURAL–DISSERTATION

zur Erlangung des Doktorgrades der gesamten Humanmedizin

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von

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## ABSTRACT

Background: Working memory (WM) impairment is a core symptom in all phases of schizophrenia (SZ). It affects different brain areas which are connected to working memory tasks. Special attention is given to the dorsolateral prefrontal cortex (DLPFC). There are different reports of hyper- and hypo-activation during a WM task. A model where the activation follows an inverted u-shaped curve has been proposed. For patients with SZ the activation is shifted to an earlier stage.

On the other hand, WM dysfunction is also a core symptom in the acute phase of a major depressive disorder (MDD), but is reported to regress in remission. Comparisons between the disorders show that there are differences in performance and activation. Those studies, however investigated a similar range of activation.

The goal of the current study is to examine differences and similarities between both disorders in a very difficult WM task. The focus is also on the activation of the brain areas underlying WM. As the DLPFC plays a major role, special attention is given to this area and the intergroup differences.

Methods: A total number of 124 subjects were selected for the present study including 42 patients with SZ, 40 with a MDD and 42 healthy control (HC) subjects. No subject was in a highly acute state of the respective disorder. All subjects underwent four behavioral tests. To investigate WM, a visual WM task was used with a baseline condition and two levels of difficulty. The task was performed in a 3-Tesla MRI scanner where the brain activation was measured. To analyze the data SPSS 21 and SPM 8 was used.

Results: In two of the four behavioral tests there were no significant differences between the three groups. In one test, SZ performed significantly worse than the two other groups and in one test MDD and SZ performed both significantly worse than the HC group. During scanning, in the 2-back task SZ performed significantly worse than both other groups, while there were no differences between the groups in the 0-, and 3-back condition. The fMRI data showed hyperactivation especially during the 2-back task in SZ in comparison

to both other groups in areas typically implied in WM. In the DLPFC hyperactivation was found in SZ and MDD compared to the HC in the 2-back task.

Discussion: The results of the study confirm the assumption that patients with SZ have a more severe WM deficiency than MDD. It appears to be a global WM dysfunction affecting various WM-related areas of the brain that only occur in SZ. However, there is a dysfunction in the DLPFC in both disorders. If we go along with the assumptions of the proposed model, we can underline a shift of the activation curve for each group.

The results of the current study contribute to the ongoing debate if there is a connection between SZ and MDD. Further investigations should have a look at MDD with psychotic symptoms and bipolar disorder and whether those disorders have similarities WM deficiencies. In the long run it could reveal a new understanding of the disorders and consequently lead to new ways in the treatment of patients.

## ABSTRACT (GERMAN)

Hintergrund: Einschränkungen des Arbeitsgedächtnisses (WM) gehören zu den Hauptsymptomen der Schizophrenie (SZ) und sind in allen Krankheitsphasen präsent. Betroffen sind unterschiedliche Hirnareale, die mit Aufgaben des WM in Verbindung stehen. Dabei liegt ein besonderer Fokus auf dem dorsolateralen präfrontalen Kortex (DLPFC). Es gibt unterschiedliche Untersuchungen, die entweder eine Unter- oder Überfunktion während einer WM-Aufgabe zeigen. Es wurde ein Modell vorgestellt, bei dem die Aktivität des DLPFC in Abhängigkeit des Schwierigkeitsgrades der WM-Aufgabe einer umgedrehten U-Kurve folgt. Bei Patienten mit Schizophrenie ist diese Kurve in einen früheren Aktivitätsbereich verschoben.

In der Akutphase einer Depression (MDD) zeigt sich ebenfalls eine Beeinträchtigung des Arbeitsgedächtnisses. Es wird jedoch berichtet, dass diese Defizite in der Remission der Erkrankung zurückgehen. Vergleiche beider Krankheitsbilder zeigen, dass es Abweichungen in der WM-Leistung wie auch in der Gehirnaktivität gibt. Diese Studien untersuchten allerdings einen ähnlichen Aktivitätsbereich.

Das Ziel dieser Studie ist Unterschiede und Gemeinsamkeiten der beiden Erkrankungen während einer sehr anspruchsvollen WM-Aufgabe zu untersuchen. Dabei wurde ein besonderer Fokus auf den DLPFC und weitere Hirnareale, die dem Arbeitsgedächtnis zu geordnet sind, gelegt.

Methoden: Für die vorliegende Studie wurden insgesamt 124 Probanden ausgewählt, darunter 42 Patienten mit SZ, 40 mit MDD und 42 gesunde Kontrollpersonen (HC). Kein Proband befand sich in einem hochakuten Krankheitszustand der jeweiligen Störung. Alle Probanden wurden vier Verhaltenstests unterzogen. Zur Untersuchung des WM wurde eine visuelle WM-Aufgabe mit einer Grundbedingung und zwei Schwierigkeitsgraden verwendet. Die Probanden befanden sich währenddessen in einem 3-Tesla-MRT. Mittels fMRT konnte die Gehirnaktivität gemessen werden. Zur Datenanalyse wurde SPSS 21 und SPM 8 verwendet.

Ergebnisse: In zwei der vier Verhaltenstests gab es zwischen den drei Gruppen keine signifikanten Unterschiede. In einem Test zeigten SZ signifikant schlechtere Ergebnisse als die beiden anderen Gruppen. Im anderen Test schnitten sowohl MDD als auch SZ signifikant schlechter ab im Vergleich zur HC-Gruppe. Während der fMRT Untersuchung zeigten SZ bei der 2-Back-Aufgabe signifikant schlechtere Ergebnisse als beide anderen Gruppen. Es gab keine signifikanten Unterschiede zwischen den Gruppen in der 0- und 3-Back-Aufgabe. Die fMRT-Daten zeigten bei SZ, während der 2-Back Aufgabe, eine Überaktivierung in Bereichen, die typischerweise mit dem WM in Verbindung stehen, im Vergleich zu beiden anderen Gruppen. Eine Überaktivierung des DLPFC wurde bei SZ und MDD im Vergleich zur HC in der 2-Back-Aufgabe gefunden.

Diskussion: Die Ergebnisse der Studie bestätigen die Annahme, dass Patienten mit SZ eine ausgeprägteres WM-Defizit im Vergleich zu MDD haben. Es scheint sich um eine globale WM-Fehlfunktion zu handeln, die verschiedene WM-bezogene Bereiche des Gehirns betrifft, die schizophrenie-spezifisch sind. Jedoch besteht bei beiden Erkrankungen eine Funktionsstörung des DLPFC. Wenn das angenommene Modell der Aktivierung des DLPFC zugrunde gelegt wird, zeigt sich eine Verschiebung der Kurve für jede Gruppe.

Die Ergebnisse der aktuellen Studie tragen zur laufenden Debatte um den Zusammenhang zwischen SZ und MDD bei. Weitere Untersuchungen sollten sich mit der Frage auseinandersetzen, ob Depressive mit psychotischen Symptomen und bipolaren Störungen ähnliche WM-Funktionsstörungen aufweisen. Langfristig könnte dies zu einem neuen Verständnis der Störungen führen und auch neue Behandlungsmöglichkeiten für Patienten offenbaren.

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## 1.1. SCHIZOPHRENIA

### 1.1.1 HISTORY

Schizophrenia is not an illness of the new age, in literature, there are many examples of psychotic symptoms. Well-known is the madness of King Lear in Shakespeare's The Tragedy of King Lear. Here Shakespeare describes many symptoms of schizophrenia, like visual hallucinations or thought disorders.[1] One of the first concepts of schizophrenia was established by Bénédict-Auguste Morel in the mid-nineteenth century, who already thought about a genetic origin of the illness.[2] Later Schneider was searching for fundamental symptoms and developed the first-rank symptoms, which were later included in the DSM-III.[3] In his description, he concentrated on phenomena that were strongly indicative of a schizophrenic disorder like commenting voices, auditory hallucinations or bizarre delusions. This is a great diagnostic tool but not intended to be an accurate description of the illness.[4]

### 1.1.2. EPIDEMIOLOGY

Today Schizophrenia is a common illness. It is present in all countries and cultures all over the world. In Germany in 2016 according to the Statistisches Bundesamt 87451 people had to be treated in hospital for schizophrenia (F20 diagnosed).[5] The prevalence of a schizophrenic psychosis is at 0,5-1% and the incidence per year is at 0,05%. Men and women have the same risk of developing the disorder. The peak age is for males at the age of 21 years, while the onset for women is a few years later.[6] Schizophrenia is a

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[1] Ottilingam, 2007

[2] Benedict Augustin Morel, 1860

[3] American Psychiatric Association, 1981

[4] M. Gelder, 2009

[5] Statistisches Bundesamt, 2018

[6] Möller et al., 2013

common disorder and with a growing population, the absolute numbers will increase in the future.

## 1.1.3. DIAGNOSTIC CRITERIA

Schizophrenia is a clinical diagnosis. The most common criteria for diagnosing schizophrenia are the DSM-V and ICD-10. While the ICD-10 is used in most European countries, in the US, DSM-V is the preferred one. Imaging methods like cranial computer tomography or brain MRI are used to exclude other disorder like cancer, ischemia or brain abnormalities. Blood tests are used to exclude acute substance abuse or metabolic imbalance. The exact criteria are listed in table 1 and 2.

**Table 1:** DSM-V major diagnostic criteria for schizophrenia

DSM-V

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Two or more symptoms for at least one month, and a minimum of one among them must be 1, 2, or 3.

1. Delusions

2. Hallucinations

3. Disorganized speech

4. Grossly disorganized or catatonic behavior

5. Negative symptoms, like diminished emotional speech

Impairment in one of the major areas of functioning for a sig. period of time since the onset of the disturbance.

Some signs of the disorder must last for a continuous period of at least 6 months.

Exclusions

Schizoaffective disorder and bipolar or depressive disorder

Direct effect of drug abuse/medication or general medical condition

If there is a history of autism spectrum disorder or a communication disorder (childhood onset), the diagnosis of schizophrenia is only made if prominent delusions or hallucinations, along with other symptoms, are present for at least one month

*Table 1 shows the major diagnostic criteria for schizophrenia in the DSM V American Psychiatric Association, 2013*

**Table 2:** ICD-10 major diagnostic criteria for schizophrenia

ICD-10

| One or more symptoms for at least one month |
| --- |
| 1. Thought echo / insertion / withdrawal / broadcasting |
| 2. Delusions of control |
| 3. Hallucinatory voices |
| 4. Persistent delusions |

| Two or more symptoms for at least one month (most of the time) |
| --- |
| 1. Persistent hallucinations |
| 2. Though block/disorder |
| 3. Catatonia |
| 4. Negative symptoms |
| 5. Significant personality change |

| Exclusion |
| --- |
| Extensive depressive/manic symptoms or diagnosis of schizoaffective disorder |
| Other brain disorder; drug intoxication/withdrawal |

*Table 2 shows the major diagnostic criteria for schizophrenia in the ICD 10 BfArM, 2021*

While first rank symptoms still play a major role in the diagnosis of schizophrenia, the negative symptoms are more relevant for the outcome and prognosis of schizophrenia.[7] Schizophrenia is divided into 6 subtypes by the ICD-10, depending on the leading characteristics of the symptoms (Paranoid, Hebephrenic, Catatonic, Undifferentiated, Residual, Simple). While positive symptoms are more present in the paranoid sub-type, the simple sub-type is characterized by the absence of positive symptoms and negative symptoms are in the foreground. In the ICD 10 GM 2021 Chapter V F00-99 is used for psychological and behavioral disorders. Schizophrenia and its sub-types are listed as F20

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[7] Amador et al., 1999

– 29. For example, F 20.0 is Paranoid Schizophrenia.[8] In the DSM V there are no subtypes of schizophrenia. [9]

## 1.1.4. SYMPTOMS

The presentation of schizophrenia is very heterogeneous. While the disorder is historically shaped by the model of Bleulers basic symptoms, like thought disorder, affective disorder or depersonalization, nowadays the positive and negative symptoms play a more important role. Positive symptoms are perceptions that add to the normal cognition. The typical example is a hallucination. Voice commenting is one of the most common hallucinations. The person believes that someone talks to him or her and comments his or her actions. Negative symptoms, on the other hand, decrease the normal cognition and/or motion of a person. The most distinct form is immobility. The person cannot move for a period of time and remains stiff. Thought processes can also be slowed down or sped up. The disorder also affects emotions.

The most common and best described symptoms are delusion, hallucination, depersonalization, thought disorder, affective disorder, and catatonia.

Delusion can be subdivided in severity. At first, there is a delusional mood. The person has the feeling something strange is going on but cannot describe it. In further states, the person is inevitable convinced of his thoughts. An abstract from a text of Manfred Kruse describes the development of delusional thought. *"1978, ...I had the feeling that someone would whisper about me. … Around the year 1981, I had the fantasy that at my neighbor's house counterpart my window a video camera was installed to observe my sleeping room. … 1983 I was attending a one-week long management seminar by my company. I felt traced/observed and thought a network of intrigues was running against me and in my personal record it would be written that I am a loser. … 1985 short after my 35 birthday I*

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[8] BfArM, 2021

[9] American Psychiatric Association, 2013

*was going through hell. For 5 days I was in a world of bizarre delusion in which I was hearing voices sometimes. I developed the horrible delusion that in my head instead of a brain a computer transmitter was installed. … Deepest desperation overcame me."*[10]

Hallucinations are also common in schizophrenia. There are different types of hallucinations depending on the effected sense. Acoustic hallucinations are most common and can occur as commenting voices or discussing voices. There are also visual, olfaction, gustatory and body feeling hallucinations.

On the other hand, self-disorder plays a major role in schizophrenia. Depersonalization and derealization are a part of this complex. The border between the person itself and the environment melts away. This can also affect the mind. Thought insertion, withdrawal, and broadcast can be the characteristic of it.

Another alternation is the formal thought disorder. This means that the thinking process itself is pathologically disturbed. Thoughts can be slow, stop abruptly, are not connected to each other or differ in many other ways from a normal thinking pattern. It gets difficult for people to follow the affected person in a conversation.

The affective behavior is also changed in people with schizophrenia. Emotional and facial expressions can be inadequate. A psychotic ambivalence can occur where opposing emotions exist at the same time. On the other hand, flat affective behavior is often described in residual stages of the disorder. Motor disorders and catatonia is another symptom complex. It can occur as catatonic stupor and mutism. The person is by full consciousness trapped in his own body and cannot move or speak. He can be shaped like a wax figure. Also, part of catatonia are negativism and stereotypy.[11]

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[10] Kruse, 2004

[11] Kahlbaum, 2013

## 1.1.5. AETIOLOGY

"One thing is certain about the aetiology of schizophrenia is that there is no single cause."[12] A major role play the genetic factors. Several studies show that the lifetime risk for schizophrenia in the average population is at about one percent and increases to about 10 percent for first-degree relatives of schizophrenia and rises to 50 percent for monozygotic twins and children with two schizophrenic parents.[13] Children of a mother with schizophrenia show cognitive and motor neurointegrative deficiency. The complex is called pandymaturation. Further investigations revealed that pandymaturation is a risk factor for developing schizophrenia or even a pre-stage of the disorder itself.[14] Many studies have tried to identify a specific gene that is responsible for schizophrenia, but so far may different genes with only a small impact have been found. It is believed that the cause lays in the interaction of many different genes. An association between a haplotype on the gene neuregulin 1 (NRG1) on chromosome 8p22-p11 and the pathogenesis of schizophrenia is found in Icelandic population and later confirmed in other populations with adjacent haplotype blocks for the Caucasian and Asian population.[15] Another gene, dysbindin (DTNBP1) on chromosome 6p22.3, is associated with schizophrenia. But none of the identified genes are proven a 100 percent to be a cause for schizophrenia.[16] [17]

Regarding twin studies it becomes clear that there must be factors other than genetics, because only 50 % of the monozygotic twins experience transitions to the disorder. Beside the genes, environmental factors, especially complications during pregnancy and birth,

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[12] Murray & Castle, 2012

[13] Gottesman, 1991

[14] Fish et al., 1992

[15] Li et al., 2006

[16] Murray & Castle, 2012

[17] Gelder, 2009

are found to play a major role in the development of schizophrenia.[18] [19] One study shows that also smoking during pregnancy is a risk factor for developing schizophrenia.[20]

It appears that children born and raised in urban areas are more likely to develop schizophrenia than children grown up in rural areas.[21] Also, immigration seems to be a risk factor for developing schizophrenia.[22] Consume of cannabis and the influence of developing schizophrenia is a controversial topic. The consumption of cannabis in vulnerable individuals can add to other risk factors and induce the disorder.[23] Also, the onset of the disorder is earlier under the influence of cannabis and a re-exacerbation is more likely.[24]

The genesis of the disorder is multifactorial. An interaction of predisposing factors (genetic factors, cerebral damage, psychosocial factors) and triggering factors (live event, hallucination) can lead to the development, although progression is dependent on different factors.[25]

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[18] Geddes et al., 1999

[19] Ambroz et al., 2017

[20] Niemelä et al., 2016

[21] Marcelis et al., 1998

[22] Cantor-Graae & Selten, 2005

[23] Arseneault et al., 2004

[24] Jockers-Scherübl, 2009

[25] Scharfetter, 1995

## 1.2. MAJOR DEPRESSIVE DISORDER

### 1.2.1. HISTORY

In the Greek empire more than 2000 years ago Hippocrates used the term melancholia to describe a syndrome consisting of sadness, dejection, and despondency. He believed in a connection between body and brain to cause this disorder. Later in the western civilization this early understanding vanished.

Persian physicians also believed in a complex interaction between body, mind, environment, and society to cause mental disorder.[26] In 1632 Richard Burton published "The anatomy of melancholy" in which he described the development of melancholic thoughts. He saw it as a disorder with two faces. On the one hand with mood elevation and on the other in low mood.[27] In his descriptions Kraepelin used the term "depression" and divides it into different categories. While he thought of the disorder as a physical disorder Freud saw the origin in mental trouble in the individual history.[28] In the Diagnostic and Statistical Manual the major depressive disorder (MDD) was first described in the third edition in 1980.[29]

### 1.2.2. EPIDEMIOLOGY

MDD is a common mental disorder. Not only in the western world but all over the globe. In Germany in 2016, there were 263 428 people who had to be treated in a hospital for Depression (F32 and F33). This means that Depression is the second most treated disorder in psychiatric hospitals.[30] In Germany, the lifetime prevalence is at 9.9 % and the 12-

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[26] Sadeghfard et al., 2016

[27] Burton, 1632

[28] Sadeghfard et al., 2016

[29] American Psychiatric Association, 2000

[30] Statistisches Bundesamt, 2017

month prevalence at 3.0 % based on the DSM-IIIR and DSM-IV criteria. Women are twice as likely to be affected as men. The mean age of onset is 27.6 years.[31]

### 1.2.3. DIAGNOSTIC CRITERIA

Depression - like schizophrenia – is a clinical diagnosis. In line with the diagnostics for schizophrenia, major depressive disorder is in the USA diagnosed on basis of the DSM V criteria. In Europa ICD 10 is used most of the time. All affective disorders are listed F30 - 39. The further division is made by the kind of mood alteration, whether it is manic, depressive, or alternating. Another important criterion is time and severity of the disorder. For example, a major depressive episode without psychotic symptoms is coded F32.2.

In the ICD 10 there are seven categories for disorders with mood alteration as the main symptom (manic episode, bipolar affective disorder, depressive episode, recurrent depressive disorder, chronic affective disorder, other affective disorder and unspecified affective disorder). In the DSM there is one chapter for depressive disorders and one for bipolar disorders. Under the category of depressive disorders there are 8 subcategories (disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication induced disorder, depressive disorder due to another medical condition, other specified depressive disorder, unspecific depressive disorder).[32] Because of the difference in classification, the number and the diagnoses vary between the systems.

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[31] Kessler & Bromet, 2013

[32] American Psychiatric Association, 2013

## 1.2.4. SYMPTOMS

One important part of MDD is the constant existence of symptoms. The affected person suffers from the symptoms every day or nearly every day. Core symptoms are depressed mood, loss of pleasure in activities, loss of energy, loss of confidence, inappropriate guilt, deficiency in concentration, sleeping disorder.[33] The symptoms can range from mild to a state of "The Feeling of Unfeelingness". Sleeping disorders and low mood occur in almost all cases, hallucination is seen only in few patients.

Other important parts of the disorder are suicidal ideation and suicide. In Germany, in 2015 10078 people died because of suicide. 7397 of them were men and 2681 women.[34] While more women attempt suicide, the suicide rate of men is higher. This is due to the fact that men more often use "hard methods" of suicide, like hanging, shooting, jumping from high altitude or jumping in front of a train, while women use more often soft methods. Taking an overdose of medications or other toxic substances are called soft methods and are survived more often. In adolescents from the age of 15 to 20 years suicide is the second most leading cause of death after accidents.[35]

## 1.2.5. AETEOLOGY

Already early in the study of depression, a hereditary component was suggested. In adoption and twin studies, it could be shown that there must be a genetic influence in the development of MDD and bipolar affective disorder.[36] [37] A meta-analysis showed however, that there are no single-nucleotide-polymorphisms which are significant for MDD.[38] More recent studies are investigating the polygenic risk and the results indicate a

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[33] BfArM, 2020

[34] Statistisches Bundesamt, 2017

[35] Statistisches Bundesamt, 2017

[36] Kessler & Bromet, 2013

[37] Mendlewicz & Rainer, 1977

[38] Ripke et al., 2013

link between MDD and a polygenic vulnerability.[39] [40] Recent studies show that a polygenic risk for MDD is associated with impairment in brain functions.[41]

The monoamine hypothesis indicates a lack of serotonin in the synapses. The theory is based on the effect of antidepressant drugs which elevate the level of serotonin and reduce the symptoms of depression. Also, a positive relation between a lack of serotonin and depression can be found.[42] However recent investigations reveal that a lack of serotonin does not lead to depression in all cases. Now it is assumed that there are multiple factors leading toward depression, one is a serotonin deficiency.[43] A genetic variation in the serotonin transporter gene (5-HT T) can reduce the level of serotonin. Again, a connection and a combination of different factors must come together for the disorder to develop. An aberration in the 5-HT T leads to a higher vulnerability for stress and therefore the combination can cause depression, but again not in all subjects.[44] Another gene related vulnerability for stress is a polymorphism for brain-derived neurotrophic factors. Influencing the development and the remodeling of the brain, this could also be shown to lead to a higher level of stress and to depression.[45]

Environmental factors play a major role. A good and stable social environment has a favorable effect and influences the symptoms of depression substantially.[46] Especially marital trouble increases the probability of depression in many ways. Pronounced introverted and extroverted behavior is supposed to lead to a higher vulnerability.[47]

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[39] Mullins et al., 2016

[40] Middeldorp et al., 2011

[41] Yüksel et al., 2017

[42] Schildkraut, 1978

[43] Jans et al., 2007

[44] Caspi et al., 2003

[45] Duman & Monteggia, 2006

[46] Kendler et al., 2011

[47] Leff, 2014

Women are more prone to develop depression than men. There are two periods where the risk is especially high, pregnancy and the post-partum period.[48] With a rising age of pregnancy, the risk is getting even higher.[49] Other reasons are unclear and further investigation is needed.

A complete list of factors influencing the onset of depression would be beyond the scope of the present investigation. It shows however that there is no single cause and there is much in the dark that must be understood.

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[48] Afifi, 2007

[49] Aasheim et al., 2012

## 1.3. SCHIZOPHRENIA AND DEPRESSION

In the ICD-10, schizophrenia and depression are clearly divided disorders with multiple subcategories. In the classification system there is no connection or overlap between them. [50] This separation has been discussed for a long time and now with better technology and advances in genetic research, it has become a recent topic again.

The group of depressive disorders features a variety of sub-types. Special attention has been given to the unipolar psychotic depressive disorder, which can be separated from the unipolar nonpsychotic depressive disorder in many ways. Some symptoms like feelings of guilt and psychomotor disturbance are more frequent in psychotic depression than in nonpsychotic.[51] Molecular genetic studies show a connection between psychotic depression and schizophrenia with shared potential risk loci for both disorders. Also genetic studies suggest an inherited vulnerability of psychotic depression shared with schizophrenia.[52]

Furthermore, there is evidence that there is an aberration of the immune system in MDD. Therefore, research has looked at the blood cytokine level. There is an increase of TNF-alpha and IL-6.[53] However these findings are not restricted to MDD. A metanalysis confirmed that TNF-alpha and IL-6 is also above the level of healthy subjects in SZ, bipolar disorder and MDD.[54]

To gain a better understanding of the disorders and to identify possible similarities recent research has looked at the connection of the brain areas. While the medial prefrontal cortex, anterior cingulate cortex, thalamus, hippocampus and cerebellum have a functional connection deficiency in SZ and MDD, there are also variations in the

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[50] BfArM, 2020

[51] Schatzberg & Rothschild, 1992

[52] Domschke, 2013

[53] Dowlati et al., 2010

[54] Goldsmith et al., 2016

connection of the following areas: prefrontal cortex, amygdala and temporal poles.[55]
There are also functional network connections deviations in SZ and MDD.[56] Further
deviations in the connection are found in the local functional connectivity with a main
emphasis in the orbital frontal cortex, but also in the primary visual, auditory, motor
cortex and supplementary motor cortex. Here SZ are most affected, followed by bipolar
disorder and MDD.[57]

Beside the above listed connections between SZ and MDD the clinical symptoms have
also been looked at. The negative symptoms in SZ can be partially separated from the
symptoms in MDD, but there are also overlapping phenomenon like anhedonia, anergia
and avolition.[58]

The similarities and overlaps between both disorders have become an intensely studied
field and many studies have dealt with this topic and looked at different scientific aspects,
but there is still no final conclusion. The idea of a multidimensional disorder model
ranging from unipolar depression over bipolar disorder to schizoaffective disorder and
schizophrenia could be the conclusion.[59]

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[55] Yu et al., 2013

[56] Wu et al., 2017

[57] Wei et al., 2018

[58] Krynicki et al., 2018

[59] Domschke, 2013

## 1.4. MEMORY

Our world is filled with an infinite amount of information. The challenging part for our brain is to sort it and keep the important information. Sometimes information is needed for a couple of seconds later (remembering a phone number), sometimes it is used weeks or months later (remembering a way to an address). Learning as an act of gathering information and changing someone's behavior is the principle of memory and vice versa.[60]

The human memory can be categorized in different ways. One way is to categorize it by the quality. Declarative memory refers to what is commonly known as knowledge. This information can be described in words, for example, historical facts, daily events, or poetry. Consciousness is important for the memorization and replication of declarative memory. On the other hand, non-declarative memory is not available to consciousness.[61] Typical examples are skills. To ride a bicycle safely is difficult and must be practiced for a long time and once learned it will not be forgotten. However, we cannot describe exactly what we learned. Also, behavior and interaction between people are based on non-declarative memory. Figure 1 gives an overview of the categories with corresponding examples.

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[60] Gross, 2010
[61] Cohen & Squire, 1980
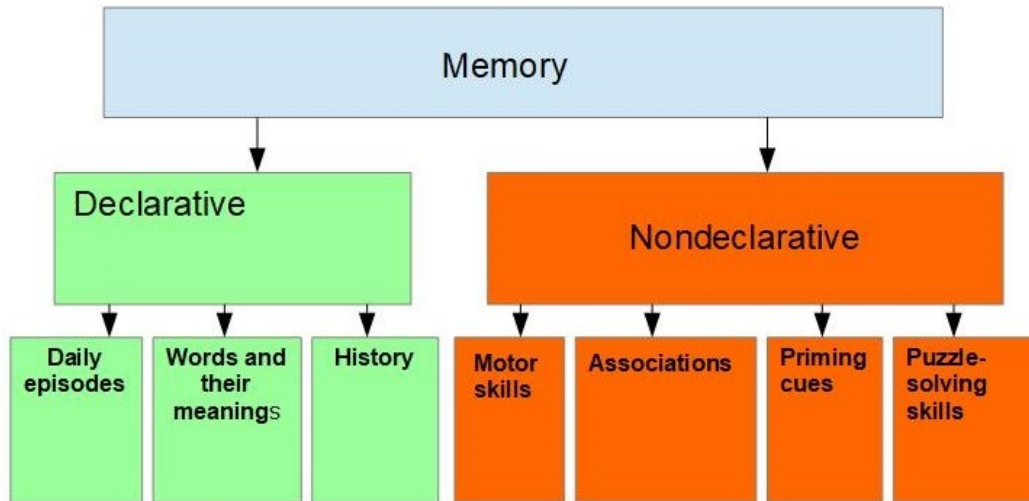
*Figure 1 shows the categorization of the memory proposed by Cohen and Squire in 1980. In their understanding, the memory can be divided into declarative and nondeclarative memory. The declarative memory is responsible for daily episodes, words and their meanings and history. On the other hand, motor skills, associations, priming cues and puzzle solving skills are a part of the nondeclarative memory.*

Another way to categorize memory is by time. A model of three systems has been developed by Atkinson and Shiffrin in 1968.[62] There is the immediate memory/sensory memory, the working/short-term memory, and the long-term memory. Each system is for a different time span. The entrance to memory is the immediate memory. It receives information gathered by the sensory systems. There is an enormous amount of information which is kept only for a very short time in the immediate memory. The capacity of the system is large, but the time span is very short. Most of the information will be forgotten but important information is passed on to the working memory or even right away the long-term memory. Usually, information from the immediate memory goes to the working memory and to enter the long-term memory rehearsal, practice or a strong emotional bond is needed. In the long-term memory information can be stored for

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[62] Atkinson & Shiffrin, 1968

days or even a lifetime. Each system has the ability to forget information as well. In figure 2 the three kinds of memory are shown and the interactions in between them.[63]

**Figure 2:** Major temporal categories of the memory
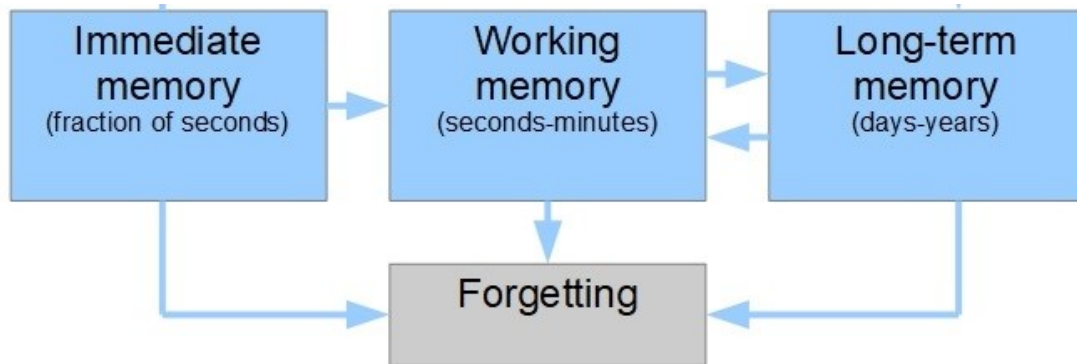


*Figure 2 shows the three different kinds of temporal memory and their connections. At first, information is in the immediate memory where it can be forgotten or moved to the working memory or long-term memory. There is a connection between the three temporal memory systems and information can shift in between. The information can also be forgotten.*

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[63] Purves, 2012

## 1.5. WORKING MEMORY

### 1.5.1. BACKGROUND

The term working memory was introduced first in the 1960s, where it was used mostly to describe what we now know as short-term memory. [64] Later the term changed its meaning. Nowadays it describes a process for taking up information from sensory systems and storing this information for further processing.[65]

There are two major theories that explain the way working memory is functioning. Baddeley and Hitch described their model first in 1974[66] and extended it in 2000. Figure 3 shows their theory which contains four units. The central executive, the phonological loop, the visual-spatial-scratchpad and the episodic buffer. The central executive guides information to the further units and grades it by importance. Furthermore, it guides attention to the sub-unite. In the phonological loop auditory information is stored by rehearsal. For example, a seven-digit number can be memorized by repeating it over and over again.[67] The visual-spatial-scratchpad can store visual and spatial information and also modify the visual image. The fourth unit, the episodic buffer, gathers information

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[64] Miller et al., 1960

[65] Miyake & Shah, 1999

[66] Baddeley & Hitch, 1974

[67] Weiten, 2013

that is not covered by other systems and is also the link between the two sub-units as well as the link between working memory and long-term memory.[68]
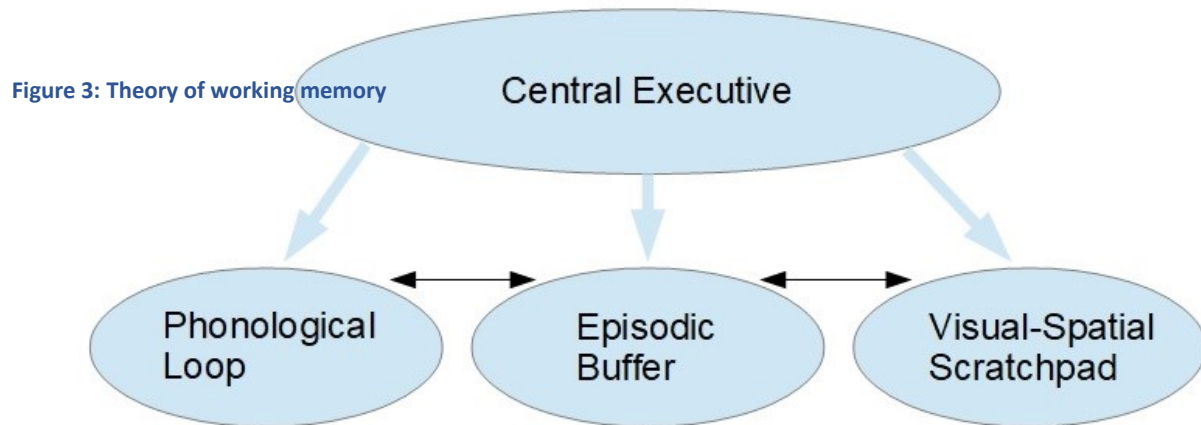
*Figure 3 shows the theory of working memory created by Braddeley and Hitch. A central executive unit passes the information to the three sub-units. The Phonological Loop receives auditory information and stores it by rehearsal. Visual information is guided to the Visual-spatial-scratchpad. Information which doesn´t fit in any of the two other sub-units is passed on to the Episodic Buffer. This sub-unit is also connected to the two other units and vice versa.*

There are other theories that see a close connection between working memory and long-term memory. Ericsson and Knitsch have developed the term long-term-working memory. In their understanding, to fulfill demanding tasks, it is essential to store and retrieve information not only from temporary memory but also from long-term memory. This includes tasks like medical diagnosing or complex text comprehension.[69]

The capacity of working memory was first described by Miller as the "magic seven". In his model seven "chunks" could be memorized and processed.[70] Later his idea was modified. It was found that the complexity of the chunks plays a major role. For example, numbers

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[68] Baddeley, 2000

[69] Ericsson & Kintsch, 1995

[70] Miller, 1956

count as easy chunks and a young person can remember seven numbers. Complex words or even unknown words are harder to remember and count as more difficult chunks.[71]

## 1.5.2. BRAIN REGIONS

The localization of the brain regions involved in working memory is still part of ongoing research. First experiments in non-humans suggested that the prefrontal cortex is primarily involved in working memory tasks. In a study with monkeys, Jacobson showed that after ablation of the prefrontal area, the performance decreased significantly in working memory tasks, involving memorization.[72] With the introduction of MRI and PET, it was possible to have a closer look at the brain activity during tasks. It could be shown that many areas of the brain are activated during working memory tasks. However, the bilateral fronto-parietal regions seem to be the "core network".[73] The areas are activated depending on the type of material used in the task and the type of task itself.[74] Basically, two parts can be differentiated. The lateral prefrontal cortex is mostly responsible for processing and manipulating information [75] while the posterior parietal cortex is responsible for storing and retrieving the information.[76]

### 1.5.2.1. DORSOLATERAL PREFRONTAL CORTEX (DLPFC); BA 46, 9

The first region to be identified playing a major role in WM is the DLPFC. It is also one of the most investigated and debated areas. At first, a connection to the short-term memory

[71] Rozniecki & Grabski, 1975

[72] Jacobsen & Nissen, 1937

[73] Rottschy et al., 2012

[74] Wager & Smith, 2003

[75] D'Esposito et al., 2000

[76] Guerin & Miller, 2011

seemed to be the key task of the brain region.[77] But this first opinion proved to be wrong. In non-humans, there are two divided areas for spatial and one for non-spatial tasks. However, this cannot be transferred to humans. The DLPFC is essential for spatial as well as non-spatial WM tasks and shows activity regardless of the stimuli. [78] [79] Further studies than tried to identify the role of this important area. One widespread theory is that the lateral prefrontal cortex is responsible for the reorganization and changes in strategy for a WM task. It could be shown that if a WM task can be structured into higher chunks, the task performance increases while the activation of the lateral prefrontal cortex also increases.[80] The same result was obtained in different WM tasks, implicating that the stimuli are not crucial for the activation of the lateral prefrontal cortex.[81] This means that by activating the lateral prefrontal cortex a strategy change is wanted to reduce WM load and therefore to increase WM performance. This theory is supported by a study investigating patients with a frontal lobe damage (excision). The patients were not able to perform a strategy change leading to poor performance in tasks where it is possible to arrange WM load into higher chunks.[82] All this evidence leads to the belief, that the lateral prefrontal cortex plays a major role in the strategy of how information is processed. A major function of the DLPFC is to reduce WM load by reorganizing information.[83]

## 1.5.2.2. POSTERIOR PARIETAL CORTEX (PPC); BA 5, 7, 39, 40

The PPC is part of the associative cortex, where information from other brain regions is brought together and proceeded. This means that it combines visual, auditory, sensory, motor and further information. The diversity of this area becomes more clearly by looking

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[77] Jacobsen & Nissen, 1937

[78] D'Esposito et al., 1998

[79] Owen, 1997

[80] Bor et al., 2003

[81] Bor et al., 2004

[82] Owen et al., 1996

[83] Owen et al., 2005

at the loss of function when it gets damaged. Balint had a closer look at patients with a PPC damage and described their symptoms. The Balint Syndrome as we know it today exists out of the triad: Simultagnosia, oculomotor apraxia, and eye ataxia.[84] As one can infer, working memory is also influenced by this part of the brain. A meta-analysis of 60 fMRI studies of WM tests found an activation of the PPC in all executive functions.[85] A further look at the exact function shows that the retrieval of information is a vital part, but the PPC also plays a major role in the limitation of scenic information. [86] [87]

### 1.5.2.3. FRONTAL POLE; BA 10

The frontal pole is activated during WM tasks. Many studies have found this activation and it has been confirmed in a meta-analysis.[88] However, the exact role of the frontal pole in WM tasks is not totally clear yet. It is postulated that this area is responsible for cognitive processes that need to keep more than one goal in mind. It is more active when sub-goals are required to successfully perform a given task. A typical example for such a task is planning or reasoning.[89] Authors of another study come to a similar conclusion. Their work shows that the frontal pole plays a major role when one cognitive process is insufficient to solve a specific problem and more than one cognitive process is required to achieve the higher behavioral goal.[90] Both skills are required to successfully perform a WM task and especially an n-back task.

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[84] Whitlock, 2017

[85] Wager & Smith, 2003

[86] Berryhill & Olson, 2008

[87] Todd & Marois, 2004

[88] Owen et al., 2005

[89] Koechlin et al., 1999

[90] Ramnani & Owen, 2004

## 1.5.2.4. SUPPLEMENTARY MOTOR AREA (SMA); BA 6

The SMA is primarily known for its role in movements, and it is described as a map of the body.[91] Planning of further movements is also a well investigated role of the SMA.[92] In addition to the important role in movements, there are other related functions. There is evidence that there is also an importance for WM tasks, although it has been little investigated. The SMA seems to be involved in WM tasks where information must be stored or held and further processed.[93] This is in part in line with a recent study showing that patients with SMA injury have a WM deficiency. The study also found that the deficiency is not only due to a reduction in processing speed. The author suggests that the deficiency is due to a lack of manipulating the information held in WM.[94]

## 1.5.3. SCHIZOPHRENIA AND WORKING MEMORY IMPAIRMENT

### 1.5.3.1. PERFORMANCE

As earlier described, schizophrenia is often associated with marked hallucination, while negative symptoms remain hidden to the broad public. For the outcome and diagnosis on the other hand, negative symptoms play a major role. Cognitive dysfunctions are a part of negative symptoms. WM performance is involved in many cognitive functions. A subdivision in verbal and spatial WM shows a deficiency in both areas for patients with schizophrenia. While visual orientation can be found in both spatial and verbal WM, other deficiencies like memory of objects are only connected to one part, in this case to spatial WM.[95] A meta-analysis of different WM tests and the related performance shows poor

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[91] Penfield & Welch, 1951

[92] Penfield & Welch, 1951

[93] Wager & Smith, 2003

[94] Cañas et al., 2018

[95] Silver et al., 2003

results for patients with schizophrenia in all areas.[96] While poor WM performance has been established in SZ, the underlying mechanisms are not explained in total yet. A limitation of the storage capacity in WM is a key point behind the symptoms and poor WM performance.[97] Processing speed is another important factor, which is reduced in SZ patients.[98] The poor performance is also a consequence of an ineffective WM system with an impaired functional output.[99]

## 1.5.3.2. FMRI (FUNCTIONAL MAGNETIC RESONANCE IMAGING) AND MRI

In 1995 deficiency of working memory was shown in patients with schizophrenia and it is believed that the DLPFC is playing a major role.[100] In 1998 Callicot et al. published the first fMRI study to examine the differences in individuals with schizophrenia and healthy controls. The results show a hypoactivation of the DLPFC and a tendency of hyper-activating the parietal cortex. However, methodological problems such as the small sample size were criticized.[101] Another study by Barch et al. shows also a deficiency in activating the DLPFC but no deficiency in other areas.[102] In a meta-analysis in 2001 hypo- and hyper-activation is found in the prefrontal cortex. Furthermore, there is a greater difference in the activation of the DLPFC in patients than in controls. Also in each individual the task performance is less constant as well as the activation pattern. The activation does not correlate linearly with the increase of working memory load. It is assumed that with the increase of working memory load, the activation also increases up to a critical point, after which it decreases again because of excessive demand. It is supposed that the activation follows an inverted u-shaped curve. For SZ the curve is

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[96] Lee & Park, 2005

[97] Silver et al., 2003

[98] Trapp et al., 2017

[99] Jansma et al., 2004

[100] Park et al., 1995

[101] Callicott et al., 1998

[102] Barch et al., 2001

shifted to the left so that activation is higher at a lower task difficulty and decreases earlier than in healthy subjects. Figure 4 is based on the figure by Manoach and shows the postulated curve progression for the activation of the DLPFC depending on the WM load.[103]

Activation DLPFC

**Figure 4:** Postulated brain-activation-WM-Load association by Manaoch
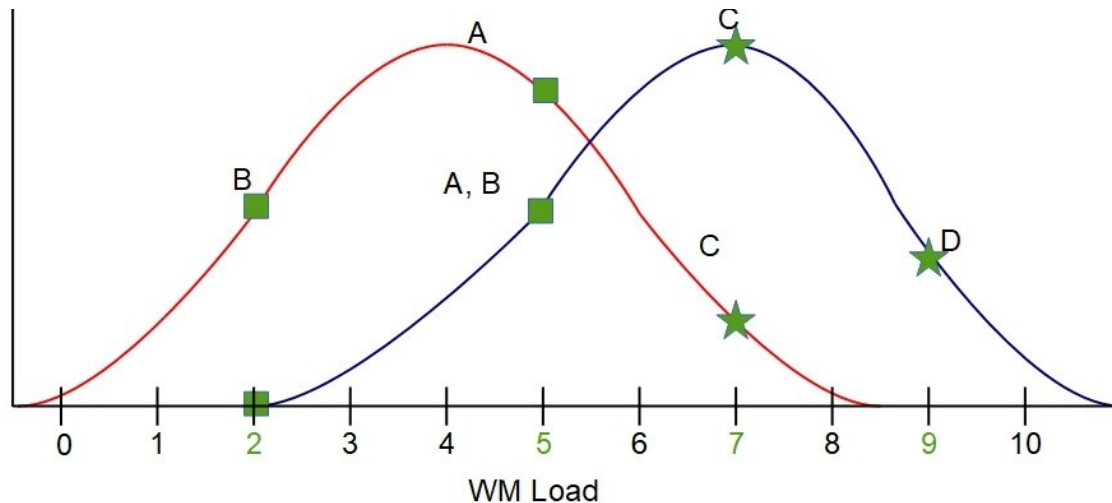


*Figure 4 is based on the figure from Manaoch, 2003. It shows the postulated activation pattern of healthy and Schizophrenic patients during a WM-task. The x-axis shows the number of targets used in the WM-task and the y-axis the activation of the DLPFC. A) SZ have a higher activation of the DLPFC during a WM task with high demand (five targets). B) SZ and HC have the same activation while HC can perform a much harder task (five instead of two targets). C and D) the asterisk mark the postulated activation during a very high demanding task.*

However, there are deviations from the hypothesis. There are studies showing SZ have a flattened curve.[104] It seems that in general an inefficient activation pattern in the DLPFC is seen in SZ patients.[105] This may occur because of a change in strategy where resources shift to other areas.[106]

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[103] Manoach, 2003

[104] Jansma et al., 2004

[105] Potkin et al., 2009

[106] Callicott et al., 2003

Recent research is looking for alterations in the connection between the different areas in SZ leading to poor WM performance. Nielson et at. shows that there is a lack of forward connection between the posterior parietal cortex and the DLPFC.[107]

Another interesting difference is seen in gray matter volume. SZ have a reduced grey matter in the DLPFC, superior temporal and superior parietal lobe reduced while there is no significant difference in other areas. The loss of gray matter is also correlated with the severity of the disorder.[108]

## 1.5.4. MAJOR DEPRESSIVE DISORDER AND WORKING MEMORY IMPAIRMENT

### 1.5.4.1. PERFORMANCE

It is well known that depression also goes along with cognitive impairment. However, studies show controversial results on the question whether there is also a deficiency in working memory. A meta-analysis of more than 113 studies shows a significant effect of depression on WM. The impairment is associated with the severity and the use of medications.[109] Especially reaction time is prolonged, and the accuracy is reduced.[110] In remitted patients, however the deficits are largely improved.[111] [112]

### 1.5.4.2. FMRI

While the performance is reduced, the pattern of brain activation also differs. Even without any task demand there is a hyper-activation in depressed patients in the ventral

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[107] Nielsen et al., 2017

[108] Cannon et al., 2002

[109] Snyder, 2013

[110] Rose & Ebmeier, 2006

[111] Minichmayr, 2013

[112] Norbury et al., 2014

medial prefrontal cortex, left ventral striatum, and left thalamus and hypoactivation in the left postcentral gyrus, left fusiform gyrus, and left insula.[113] While performing a working memory task the prefrontal and parietal gyrus are hypo-activated.[114]

## 1.5.5. DIFFERENCES BETWEEN SCHIZOPHRENIA AND MAJOR DEPRESSIVE DISORDER IN WORKING MEMORY

The link between MDD and schizophrenia is an ongoing subject of research in recent years. Members of families with a schizophrenic disorder show not only a higher risk of developing schizophrenia but also of a mood disorder.[115] Techniques to investigate the genetic influence on disorder made it possible to look for links. A variation on the GABA(A) receptor gene seems to play a role in the development of both disorders. Altered brain activation is also present in both disorders with similarities and a hypofrontality.[116]

On the basis of the scientific knowledge, the question is already asked if a hard diagnostic line between the two disorders can even be drawn.[117]

With this background in mind, a closer look at the differences and similarities of WM in both disorders can give some further knowledge.

A clear difference between SZ and MDD and healthy controls can be found in a study by Barch et al. in 2003. In a WM task with a 2-back paradigm, the SZ performed significantly worse than the two other groups. In the activation, there is also a greater difference between schizophrenic patients and the other groups and no major similarity between SZ and MDD. The activation of the right DLPFC was low in SZ while the activation in MDD was

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[113] Kühn & Gallinat, 2013

[114] Dumas & Newhouse, 2015

[115] Baron & Gruen, 1991

[116] Medved et al., 2001

[117] Craddock et al., 2009

in line with healthy controls.[118] Also, a difference can be found in the mPFC where SZ differ from bipolar disorder and HC again.[119] Further investigations show similar results while hypo- and hyper-activation seems to depend on the task demand following an inverted u-shaped curve. [120] [121] While some relationship can be found between schizophrenia and psychotic mood disorder, patients with a psychotic mood disorder tend to have a greater impairment than patients without psychotic symptoms.[122]

With the results of the current research, we can predict the activation of the DLPFC for MDD compared to HC and SZ. In line with the proposed inverted u-shaped curve by Manoach, it can be expected that the curve of MDD is between the HC and SZ. According to present studies, MDD without psychotic symptoms should show a higher activation of the DLPFC at an easier task than HC but not as much as SZ. The turning point should be reached at a higher task demand compared to SZ. A slight left shift of the curve would be the result.

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[118] Barch et al., 2003

[119] Milanovic et al., 2011

[120] Palaniyappan & Liddle, 2014

[121] Birur et al., 2017

[122] Brandt et al., 2014

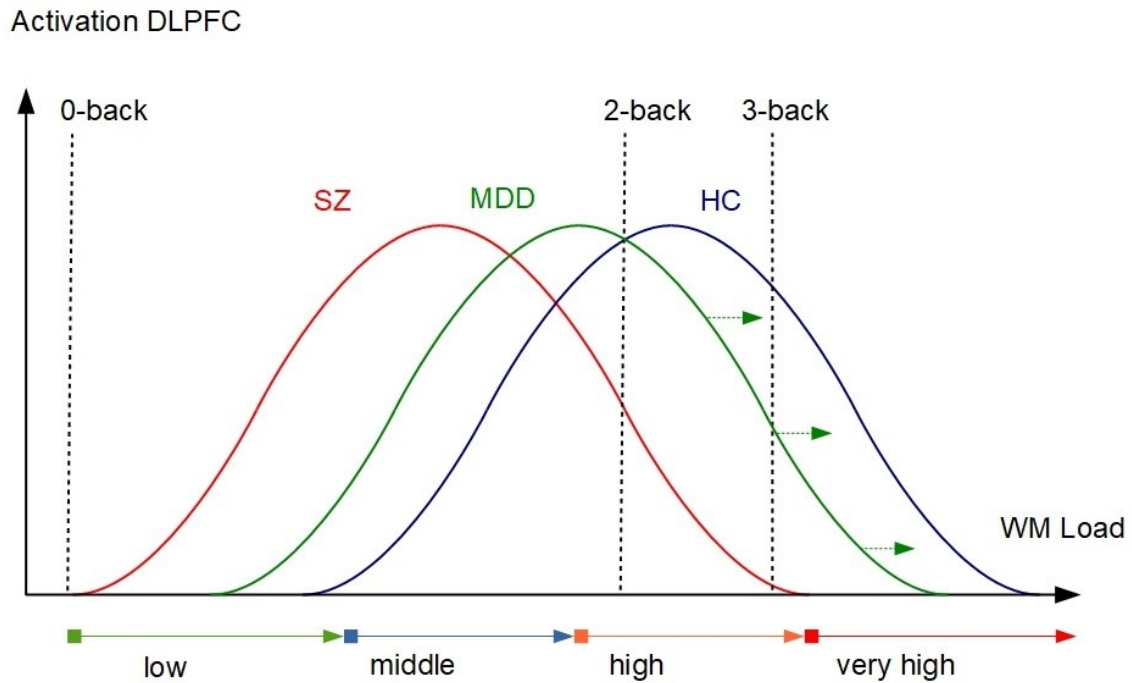*Figure 5 shows the expected activation differences of the DLPFC regarding the task difficulty. The inverted u-shape curve is based on the assumption of Manoach et. al. for HC and SZ patients. Our goal is to investigate whether the expected hypo activation occurs at a 3-back task in SZ patients. Furthermore, we examine if MDD patients are more in line with HC or if they have also a significant WM deficit as SZ patients do.*

## 1.6. HYPOTHESES

The aim of the current study is to specifically investigate the differences and similarities in WM in SZ and MDD compared to HC. On the background of the current publications and research the following hypotheses were set.

### 1.6.1. BEHAVIORAL DATA

A) A decrease in cognitive performance in WM is predicted for SZ and also for MDD patients. Cognitive performance of all groups will be assessed with several behavioral test. HC should perform best in all cognitive tasks followed by MDD and SZ patients.

### 1.6.2. N-BACK DATA

B) The subjects performed an n-back test with an increasing difficulty. As the task is getting more and more difficult, less accuracy and an increase of reaction time is expected for all groups. As there should be a previously described deficiency in WM task for SZ patients it is expected that this group will perform less accurate and with a slower reaction time than the HC. The deficiency in WM is not as clearly described in MDD. As the sample consists of MDD patients without psychotic symptoms, a performance difference between the two other tested groups is expected.

### 1.6.3. FMRI-DATA

C) In line with the predictions of the performance in the n-back task alteration in the activation of brain areas related to WM are expected. Patients with SZ should show an alteration compared to both other groups. Only marginal differences between MDD and the other groups are expected.

D) Special attention is given to the DLPFC. Manoach et. al. predicted that the activation pattern of this area follows an inverted u-shape.[123] The highest level of activation is expected at a difficult task. If WM capacity is exceeded because the task is too difficult the activation is supposed to decrease. So, a 2-back condition was chosen as a difficult task and a 3-back condition as a very difficult task. For HC the activation should be high during the 2-back task and increase during the 3-back. For SZ patients the inverted u-shaped curve should shift toward the left and have the peak of activation at a lower task difficulty. Regarding this hypothesis, hyper-activation during the 2-back task and hypo-activation during the 3-back task should occur when comparing SZ to both groups.

While MDD patients should perform slightly worse than HC controls, they still should show an activation pattern that is more in line with HC than with SZ patients. Therefore, we do not expect an alteration for this group compared to the other groups. The inverted u-shaped curve is expected to be slightly shifted to the left side. Especially because all patients have no psychotic symptoms, no close connections to the SZ group are expected.

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[123] Manoach, 2003

## 2. METHODS

### 2.1. SUBJECTS

The participants were recruited in Marburg, Germany by online and newspaper advertisement, patients were inpatients of the Dept. of Psychiatry Marburg. For the present study 124 subjects were selected. The subjects were divided into three groups. The HC group consisted of 42 subjects. The two groups of interest were the major MDD group with a total of 40 subjects and the SZ group with 42 patients. All patients were classified according to ICD-10. The SZ group with 42 subjects consisted out of 35 patients with an F20. diagnosis, 7 patients were diagnosed F25. for a schizoaffective disorder. In this group, 4 patients had a psychotic secondary diagnosis and 7 a comorbidity. The MDD group consisted of 40 patients of whom 16 were diagnosed either F31.1 or F31.2 and 23 were diagnosed with F33.1 or F33.2. 8 were diagnosed with an F34.1 as a secondary diagnosis. Comorbidities persisted in 15 patients. None of the MDD or HC subjects had psychotic symptoms. The main and secondary diagnosis as well as the comorbidities are listed in table 3 for MDD and in table 4 for SZ.

**Table 3:** Diagnoses of the major depressive group

| Main Diagnosis | Number of subjects | Percentage |
|---|---|---|
| F32.1 | 8 | 20.0 |
| F32.2 | 8 | 20.0 |
| F33.1 | 10 | 25.0 |
| F33.2 | 13 | 32.5 |
| F32/33 | 1 | 2.5 |
| **Sum** | **40** | **100.0** |

| Secondary Diagnosis | | |
|---|---|---|
| F34.1 | 8 | 20.0 |
| **Sum** | **8** | **20.0** |

| Comorbidities | | |
|---|---|---|
| F40.01 | 1 | 2.5 |
| F41.0, F43.1 | 1 | 2.5 |
| F60.5 | 1 | 2.5 |
| F60.6 | 1 | 2.5 |
| F60.7 | 1 | 2.5 |
| F60.8 | 3 | 7.5 |
| F63.8 | 1 | 2.5 |
| F10.1 | 1 | 2.5 |
| F17.2 | 5 | 12.5 |
| **Sum** | **15** | **37.5** |

*Table 3 shows the diagnose by the ICD-10 classification. It shows also the secondary diagnose, as well as the comorbidities for each group. The number and percentage of the whole group is given. If a person had multiple comorbidities it is listed for one person.*

**Table 4:** Diagnoses of the schizophrenia group

| Main Diagnosis | Number | Percentage |
| --- | --- | --- |
| F20.0 | 32 | 76.2 |
| F20.3 | 1 | 2.4 |
| F20.6 | 2 | 4.8 |
| F25.0 | 2 | 4.8 |
| F25.1 | 3 | 7.1 |
| F25.2 | 1 | 2.4 |
| F25.9 | 1 | 2.4 |
| **Sum** | **42** | **100.0** |
| | | |
| **Secondary Diagnosis** | | |
| F33.1 | 1 | 2.4 |
| F41.0 | 2 | 4.8 |
| F60.3 | 1 | 2.4 |
| **Sum** | **4** | **9.5** |
| | | |
| **Comorbidities** | | |
| F10.0, F10.1, F17.2 | 1 | 2.4 |
| F12.2 | 1 | 2.4 |
| F17.1 | 1 | 2.4 |
| F17.2 | 2 | 4.8 |
| F19.1 | 1 | 2.4 |
| F19.2 | 1 | 2.4 |
| **Sum** | **7** | **16.7** |

*Table 4 shows the diagnoses of the schizophrenia group, by the ICD-10 classification. As well as the secondary diagnose and the comorbidities for each group. The number and percentage of the whole group is given. If a person had multiple comorbidities it is listed for one person.*

The two groups were matched with 42 healthy controls out of a sample of 172 and selected with the optimal matching algorithm implemented in the MatchIt package for R (version 2.13.1, http:/www.r-project.org). Matching parameters were sex, age, and estimated verbal IQ.

Age was between 18 and 57 years with an average of 35 years. The whole group included 45 females and 79 male subjects. The education level was estimated by the highest education of each individual. Most subjects had an education level 3, followed by level 2 and 6. (0=no degree, 1=comprehensive school, 2=certificate of secondary education, 3=general certificate of secondary education, 4=vocational diploma, 5=grammar school, 6=completed studies). The IQ was estimated with the MWT-B test[124] and averaged at 106.8 (SD 12.0). Table 5 shows summary of the entire group.

**Table 5:** Basic participants information

| Total | HC | MDD | SZ | Male/Female | Age | Majority Education | Est. IQ |
|-------|-----|-----|-----|-------------|------|--------------------|---------|
| 124 | 42 | 40 | 42 | 63.7 | 34.83 (11.344) | 3 | 106.8 (12.0) |

*Table 5 shows the total number of subjects and the size of each group (HC=healthy controls, MDD=major depression disorder, SZ=schizophrenia), the male to female ration, the average age, the majority education level of the subjects and the estimated verbal IQ.*

All healthy control participants underwent a German SKID (Structured Clinical Interview for DSM IV) testing to exclude any mental disorder.

All subjects were specifically asked if they were receiving any neurological medication. If they were taking antipsychotic drugs the chlorpromazine equivalent was calculated. Table 6 shows the summary for medication intake and the CPZ equivalent for each group. In the HC group, no one was treated with antidepressant or neuroleptic drugs. In the MDD group, 35 subjects were taking antidepressant drugs. 11 subjects were also using neuroleptic drugs and averaged at a CPZ-equivalent of 140. 11 Subjects in the SZ group were taking antidepressant drugs. Neuroleptic drugs were taken by 28 subjects. The group averaged a CPZ-equivalent of 542.

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[124] Lehrl et al., 1995

**Table 6:** Medications taken by the groups

| | n | 1 NL | >1 NL | CPZ-equi. | 1 AD | >1 AD | 1 MS | >1 MS |
|---|---|---|---|---|---|---|---|---|
| **HC** | 42 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **MDD** | 40 | 11 | 0 | 140 | 28 | 7 | 0 | 0 |
| **SZ** | 42 | 23 | 15 | 542 | 10 | 1 | 5 | 1 |

*Table 6 shows the number and kind of psychiatric drugs which were taken by the different groups. Each group of medication (NL=neuroleptic drugs, AD=antidepressant drugs, MS=mood stabilizers) is divided into two rows. One for single (1) use and one for multiple (>1) use. The chlorpromazine-equivalent (CPZ-equi.) is averaged for the subjects taking one or more neuroleptic drugs.*

Subjects were excluded from the study if they had other major psychiatric disorders diagnosed other than MDD and SZ. Also, major somatic or neurological disorders were excluded as well as brain abnormalities or severe head injuries in the past. Subjects were also asked for drug or substance abuse and if positive at the time excluded from the study. For a better comparability, the subjects had to be right-handed and native German speakers. If the individuals were moving too much during the MRI scan, they also had to be excluded. For safety reason subjects did not have metal parts in their body or large tattoos. The protocol for the present study was approved by the local ethics committee according to the declaration of Helsinki. Before participation, all subjects subscribed a letter of agreement after a comprehensive disclosure.

## 2.2. BEHAVIORAL TESTS

In addition to fMRI scanning, all subjects underwent further neuropsychological tests. We used a test batterie of four tests which are explained in detail in the following.

To evaluate verbal working memory the Letter-Number-Span test[125] was used. In this test the subjects had to sort numbers and letters in an ascending order. The test started with one letter and one number and got more difficult by adding a number or a letter.

The visual working memory was tested with a Spatial-Span Test. We used the Corsi Block Test where a board with nine blocks was shown to the subject. The instructor taped several blocks in a given order and the subject had to tap the blocks in the same order. After every correct cycle one more block was added. After the first round a second-round followed were the subject had to tap the block in reversed order.[126]

Furthermore, the Digit-Symbol-Coding-Test[127] was applied for testing the information processing speed, processing efficiency as well as a screening parameter for neuropsychological dysfunction.[128] [129]

Also, a test for processing speed and a screening parameter for neurological impairment, the Trail-Making-Test (TMT) was used. For the final result of the TMT, TMT-A was subtracted from TMT-B.[130]

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[125] Gold et al., 1997

[126] Wechsler, 1997

[127] Wechsler, 1997

[128] Bachman et al., 2010

[129] Rössler et al., 2015

[130] Wechsler, 1997

## 2.3. N-BACK TEST

We use a version of the n-back test, where a single capital letter is presented for 1 second following 500 ms of a blank screen. The letters were presented in a pseudo-randomized order. Three conditions were used for this study, 0-back, 2-back, and 3-back. Each condition was presented in a block containing 12 letters. The 0- and the 2-back block had 4 response targets, while the 3-back block had only three targets. The order of the blocks was pseudo-randomized. Each task appeared twice.

The subjects had to respond on a keyboard which was fixed on the upper right leg and used by the right hand. The left button was pressed by the index finger and represented the control button while the right button presented the target and was used by the middle finger.

At the 0-back condition, letters and X´s were shown. Each time a letter appeared the subject should press the control (left) button. When an X appeared the target (right) button should be pressed. The letters were used as a control response and X as a target response. This task was used as a baseline condition. At the 2-back condition, letters were shown in a pseudo-randomized order. Subjects had to press the control button for each letter and the target button when the letter was the same as shown two letters before. At 3-back condition, the target button should be pressed when the letter was the same as shown three letters before. The task was explained personally to all participants and tested if the task was understood before the test. Directly before the task, a written explanation appeared on the screen and before each block the condition was shown. The whole test consisted out of three conditions (0-, 2-, 3-back). Each condition contained two blocks. Figure 6 illustrates the task for each condition with a time line, and the correct response.

**Figure 6:** Paradigm of the n-back task

## 0-back condition
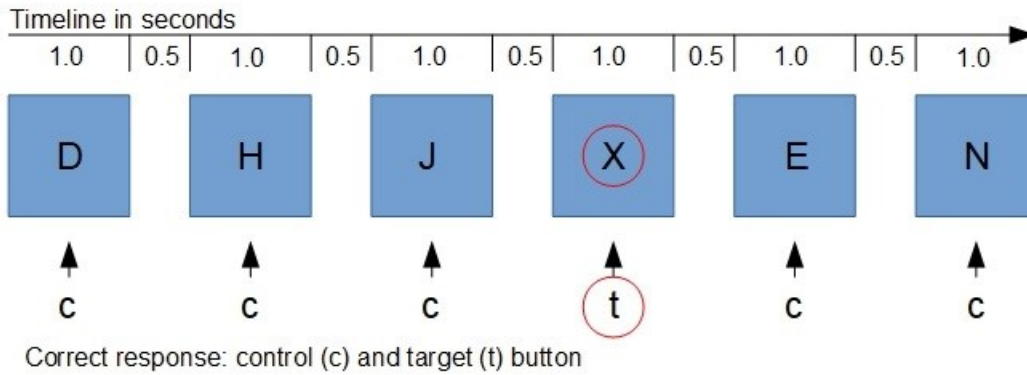


## 2-back condition
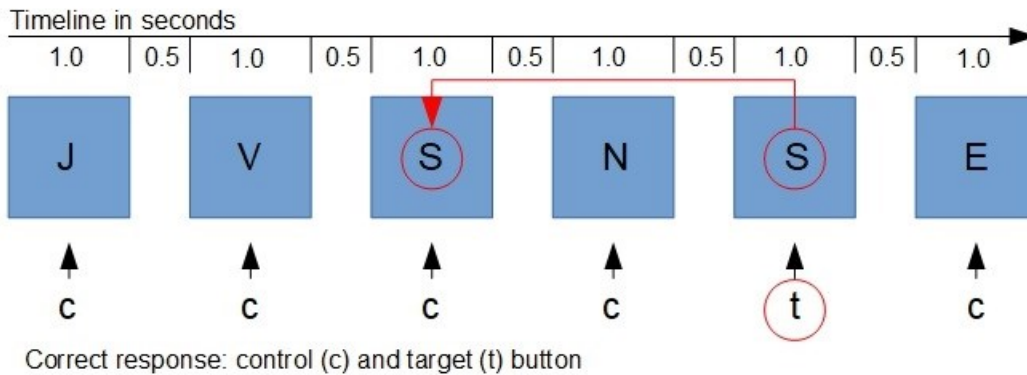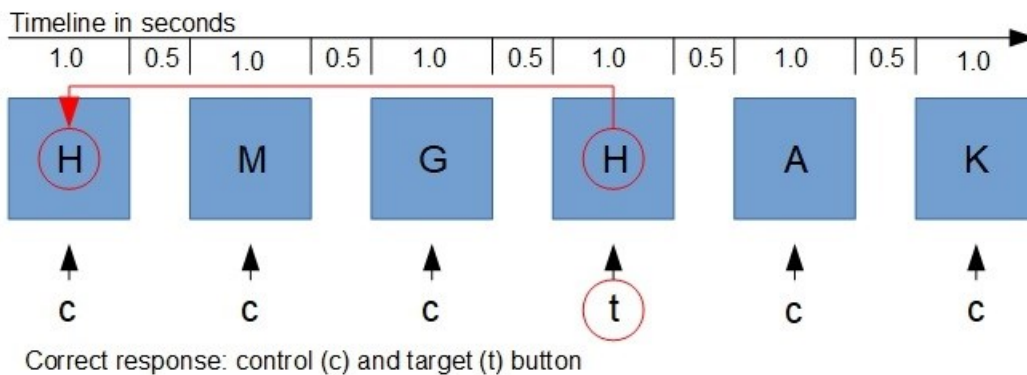


## 3-back condition



*Figure 6 shows the n-back paradigm in a 0-, 2-, and 3-back condition. In the blue square is the pseudo-randomized letter, which is shown on the screen. Above is a timeline. Every letter is presented for 1 second. Below is the correct response with c for control and t for target. The target is encircled and in the 2- and 3-back task marked to the referred letter.*

## 2.4. FMRI DATA

FMRI scanning took place at the Department of Psychiatry and Psychotherapy, Philipps-University Marburg on a 3 Tesla Tim Trio MR built by Siemens Medical Systems. A T2*-weighted echo-planar imaging (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast (64 * 64 matrix, 224 mm * 224 mm FoV, 40 slices, 3.5 mm slice thickness, TR = 2.5 s, TE = 30 ms, flip angle = 90°) was used to gather the functional data. The whole brain was scanned and positioned transaxially parallel to the anterior–posterior commissural line (AC–PC). We excluded the initial three of 160 gathered functional images from further analysis to eliminate the influence of the T1 stabilization effects.

Each person was stabilized with foam padding in the MRI to reduce head movement. Nevertheless, head movement was checked and controlled for translation and rotation movement. All participants had a translation smaller than 2,5 mm and a rotation smaller than 2,5 degrees.

The task was presented on a screen placed outside the MRI which reflected in a mirror placed in sight of the subjects. To present the task the Presentation software package (Neurobehavioral Systems, Inc. San Francisco) was used. Patients wearing glasses were given special non-magnetic glasses with the correct vision and controlled if they could see correctly.

## 2.5. DATA-ANALYSES

### 2.5.1. BEHAVIORAL DATA

SPSS in version 21 (http://www.ibm.com/software/de/analytics/spss/) was used for analyses of behavioral data. Before the analysis age and gender was checked against the diagnose in a univariate analysis. After the process age and gender was used for the further calculations as a covariance. A univariate analysis of covariance was used to calculate the behavioral data: Estimated verbal IQ, education, Spatial Span, Letter-Number-Span, Digit-Symbol-Coding, and Trail-Marking-Test.

Also, the n-back data was analyzed using a univariate analysis with age and gender as a covariance. The correct response of the 0-, 2-, and 3-back task was calculated as well as the response time for each task.

### 2.5.2. FMRI DATA

For analyzing the fMRI data SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used. A conjunction analysis was performed with a conjunction/global null hypotheses. The images were realigned and normalized to a voxel size of 2x2x2mm³ to fit the standard MNI (Montreal Neurological Institute). Furthermore, a full-width-at-half-maximum (FWHM) Gaussian smoothing mask was applied to increase the signal-to-noise ratio and to compensate for the inter-subject anatomical variation. Images and Graphics were created with the MRICRON software (http://people.cas.sc.edu/rorden/mricro/index.html) by C. Rorden in the version 1 June 2015.

# 3. RESULTS

## 3.1. SOCIO-DEMOGRAPHIC DATA

The HC group was matched to the MDD and the SZ group in sex, age, and estimated IQ. Due to this, there was no significant difference between the groups. For details see table 7. The level of highest education showed no significant difference.

**Table 7:** Social demographic data

| | HC (n=42) | MDD (n=40) | SZ (n=42) | F | p |
|---|---|---|---|---|---|
| **Gender** | | 1 | | | |
| Male | **27** (64.30%) | **25** (62.50%) | **27** (62.50%) | | |
| Female | **15** (35.70%) | **15** (37.50%) | **15** (35.70%) | | |
| **Age** | | | | | |
| Min. | 19 | 19 | 18 | | |
| Max | 57 | 55 | 57 | | |
| Average | **33.14** (11.121 SD) | **37.35** (12.162 SD) | **34.12** (10.583 SD) | 1.548 | n.s. |
| **IQ** | | | | | |
| Min. | 91 | 85 | 85 | | |
| Max | 136 | 130 | 136 | | |
| Average | **106.88** (11.802 SD) | **106.55** (9.808 SD) | **106.95** (14.187 SD) | .269 | n.s. |
| **Education** | | | | | |
| Min. | 2 | 1 | 0 | | |
| Max | 6 | 6 | 6 | | |
| Majority | **3** (17) | **3** (13) | **3** (17) | | |

*Table 7 shows the social demographic data for 42 HC, 40 MDD, and 42 SZ subjects. For each group the number of female and male subjects are given and the percentage of the group in parenthesis. For age, a univariante analysis was performed without covariance. For the IQ (estimated verbal IQ) the result was controlled with age and gender as a covariance. For education the majority with numbers in parenthesis is given. The mean values for each group, as well as the minimum and maximum is given. The standard deviation (SD) is in parenthesis. The p-value cut-off is < .05. There were no sig. differences between the groups at the age, IQ and education. The level of education was rounded.*

## 2.2. BEHAVIORAL DATA

All four tests revealed that HC performed best followed by MDD and SZ, but not all tests showed a significance in their result. There was no significant difference between the groups in the Spatial-Span test, but there was a significant difference in the Letter-Number-Span test as well as at the Digit-Symbol-Coding test, while the Trail-Marking-Test showed again no significant difference.

In the LNS, HC performed significantly better than SZ, while there were no other significant differences between the patient groups in this task. The DSCT revealed a significant difference between all groups. HC performed significantly better than MDD and SZ. MDD again performed significantly better than SZ. Table 8 lists the exact results for each task and each group as well as the F- and -value.

**Table 8:** Behavioral data

|  | HC | MDD | SZ | F | p |
|---|---|---|---|---|---|
|  | MV/SD | MV/SD | MV/SD |  |  |
| **SS** | 16.45/3.3 (42) | 16.35/3.3009 (40) | 16.05/3.162 (42) | .43 | n.s. |
| **LNS** | 15.26*/3.335 (42) | 14.65/3.534 (40) | 13.31*/3.699 (42) | 3.485 | **< .05*** |
| **DSCT** | 60.17*/10.426 (41) | 53.55*/9.276 (40) | 46.49*/8.035 (41) | 23.816 | **< .05*** |
| **TMT** | 31.9048/17.29487 (42) | 35.775/20.29335 (40) | 40.7317/24.76189 (41) | 1.767 | n.s. |

*Table 8 shows the behavioral data with the Spatial-Span (SS), Letter-Number-Span (LNS), Digit-Symbol-Coding-Test (DSCT) and Trail-Marking-Test (TMT). Each test was calculated with the number of subjects given and corrected with age and gender as a covariance. The mean value, as well as the standard deviation, is given for each group. The F value is shown. The p-value with a cut-off < .05 shows if there is a significance difference. *At the LNS HC performed sig. better than SZ. At the DSCT HC performed sig. better than MDD and SZ and MDD also performed sig. better than SZ. (MV mean value, SD standard deviation)*

## 2.2.3. N-BACK DATA

The 0-back test was used as a baseline condition. HC responded correctly with an average of 88.62 % (SD=20.15%). MDD had a slightly better average at 91.45% (SD=10.60%) and the SZ slightly worse at 85.31% (SD=19.45%). There were no significant differences between the groups. The 2-back test showed a significant difference between the groups. HC performed significantly better at 79.40% (SD=19.03%) compared to SZ with an average of 68.10% (SD=23.60%). MDD were in between with an average of 74.30% (SD=18.16%). There was no significant difference between the HC and MDD and between the MDD and SZ. Again, no significant difference was seen at the 3-back test. Here HC (58.29%, SD=22.71%) and MDD (58.28%, SD=22.64) averaged almost the same while SZ performed slightly worse (50.02%, SD=24.19%) but not significantly. The reaction time was also taken and compared but showed no significant difference at any task. The time prolonged for each group with the increase of the difficulty level. The reaction times, as well as the percentage of correct answers, are shown in table 9.

**Table 9:** Results of the n-back task

| | HC (n=42) | SD | MDD (n=40) | SD | SZ (n=42) | SD | F | Sig. |
|---|---|---|---|---|---|---|---|---|
| **Correct answers in percent** | | | | | | | | |
| 0-back | .8862 | .20149 | .9145 | .10597 | .8531 | .19453 | 1.551 | n.s. |
| 2-back | .79* | .19 | .743 | 18.163 | .681* | .23596 | 3.14 | < .05* |
| 3-back | .5829 | .22714 | .5828 | .22638 | .5002 | .24185 | 1.96 | n.s. |
| | | | | | | | | |
| **Mean response time in ms** | | | | | | | | |
| 0-back | 5223 | 857 | 5540 | 1189 | 5714 | 1456 | 1.691 | n.s. |
| 2-back | 7111 | 1816 | 6834 | 1374 | 7541 | 2057 | 1.805 | n.s. |
| 3-back | 7386 | 1781 | 7419 | 1657 | 7983 | 2593 | 1.161 | n.s. |

*Table 9 shows the percentage of the correct target responses for each group and each condition. The standard deviations (SD) is shown, as well as the F-Test (F) for each condition. The significance level of p< .05 is undercut only by the 2-back condition. *(HC performed sig. better than SZ) All other conditions have a p-value of p> .05 and are therefore not significant (n.s.). The mean response time is also shown and the SD for each response. No significant difference was found. All tests were controlled by age and gender as a covariance.*

## 2.4. FMRI-DATA

### 2.4.1. 0-BACK VS. 2-BACK CONDITION

When the baseline condition was compared with a difficult WM condition there were several significant differences in the activation of brain regions. Lower activations could be seen in the HC group compared to the other groups in the inferior frontal gyrus, which is shown in figure 7. When comparing SZ with the other group's hyper-activation was shown in the following areas: SMA, paracentral lobule, superior frontal gyrus and the supra marginal gyrus. This is illustrated in figure 8.

*The figures below (figure 7 – 11) show the area of the significant difference in the brain activation in the corresponding task between the groups. The area is marked red for hyper- and green for hypo-activation. In the lower right corner is a brief description with the n-task (0-b = 0-back task), the groups which are compared and the name of the brain region where the area is located. In the upper left corner is the coronal view, in the upper right corner the sagittal view, and in the lower left corner the axial (S = superior direction; P = posterior direction, A = anterior direction; L = left direction). The coordinates are in the MNI system.*

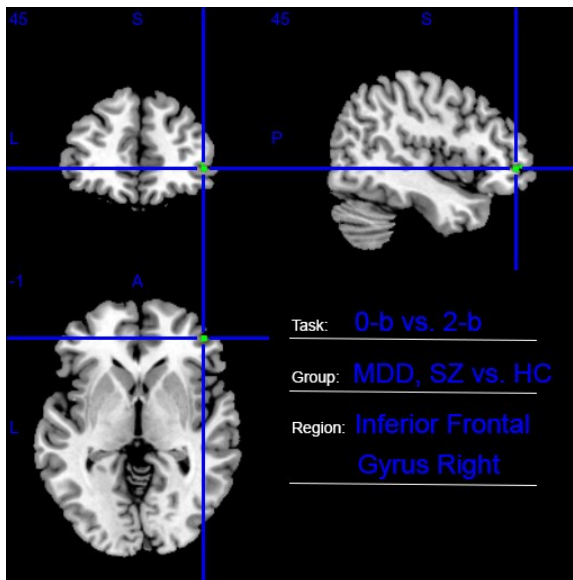**Figure 7:** 0-back vs. 2-back condition



*Figure 7: There is a significant hypo-activation in the inferior frontal gyrus in the right hemisphere in HC compared to MDD and SZ. The 0-back task is compared to the 2-back task.*
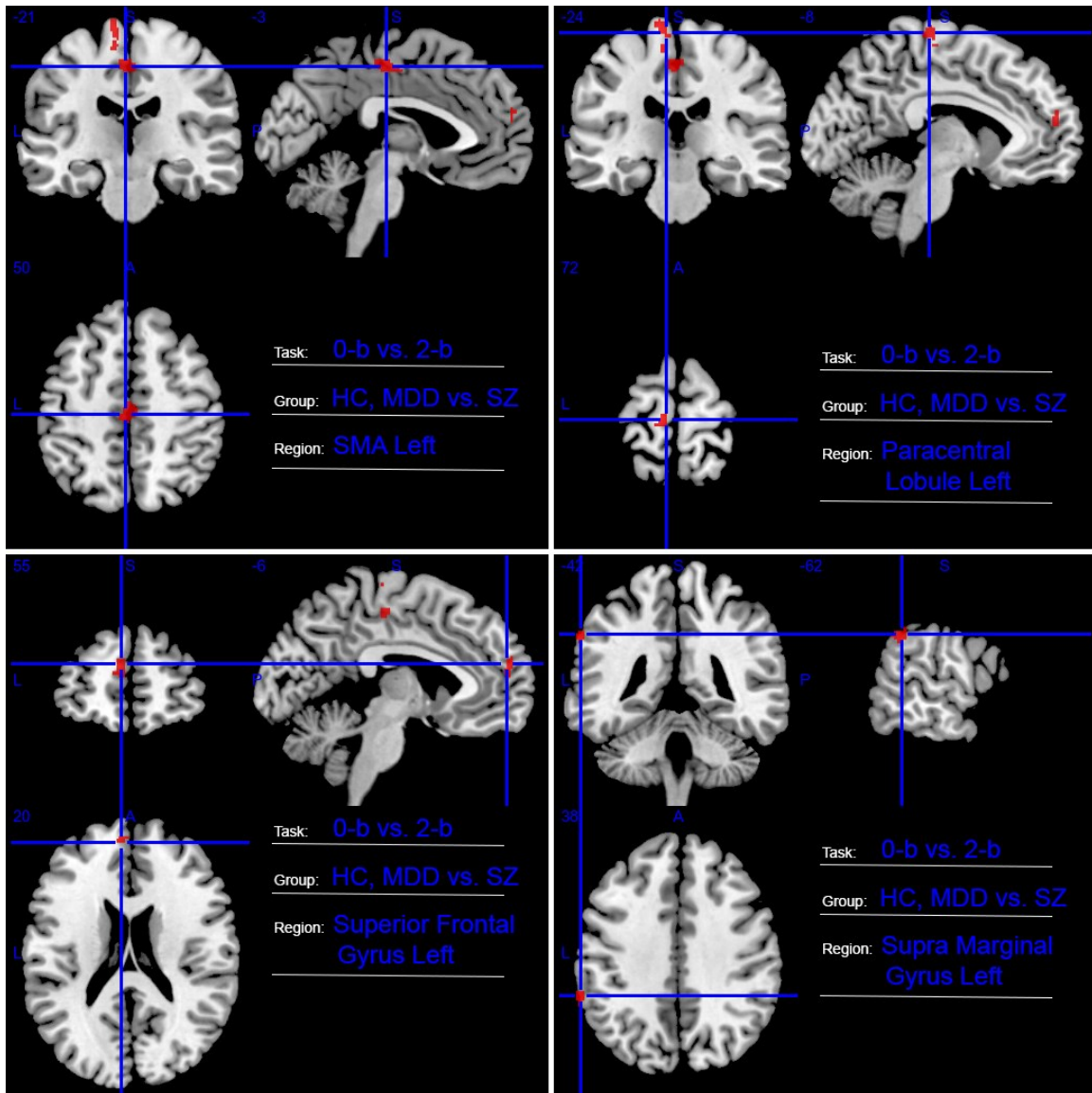
**Figure 8:** 0-back vs. 2-back condition



*Figure 8: SZ show a significant hyper-activation in four areas when compared to HC and MDD during a 0-back compared to a 2-back condition. The areas are all located in the left hemisphere. In decreasing order of the number of clusters: supplementary motor area (SMA), paracentral lobule, superior frontal gyrus and supra marginal gyrus.*

## 2.4.2. 0-BACK VS. 3-BACK CONDITION

By comparing the baseline condition with a very high demanding task there were three clusters which showed significant differences when comparing the HC and MDD groups with the SZ group. Figure 9 presents the areas of interest which showed hyper-activation in the middle temporal gyrus on both sides as well as in the postcentral gyrus.
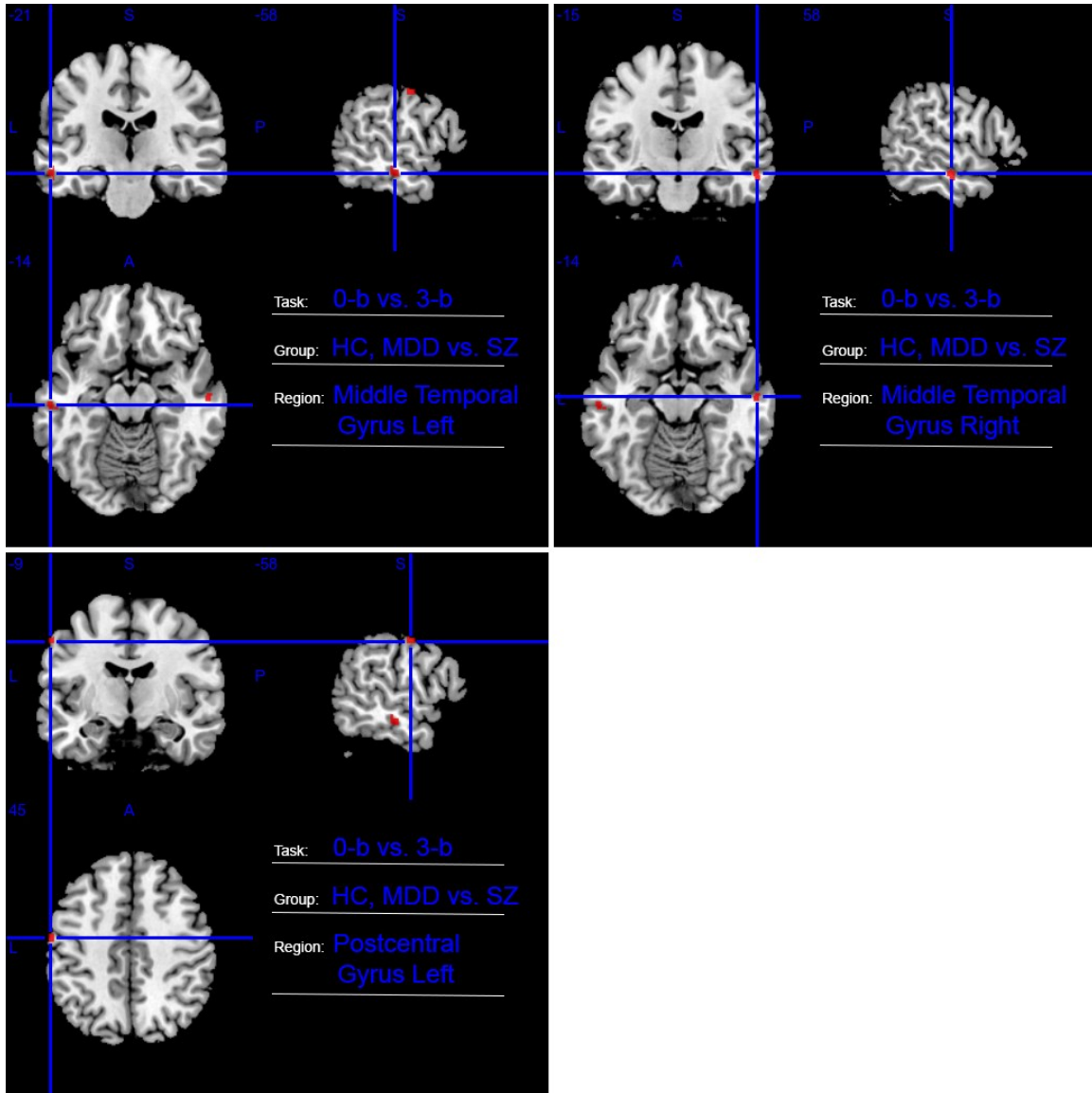
**Figure 9:** 0-back vs. 3-back condition



*Figure 9: Also a hyper-activation is found in SZ compared to HC and MDD in the 0-back compared to the 3-back condition. There is a significant difference in the middle temporal gyrus in the left and right hemisphere as well as in the postcentral gyrus on the left side.*

### 2.4.3. 2-BACK VS. 3-BACK CONDITION

When a high demanding task was compared with a task of very high demand there was significant hyper-activation in the cerebellum in the SZ group compared to both other groups which is presented in figure 10.

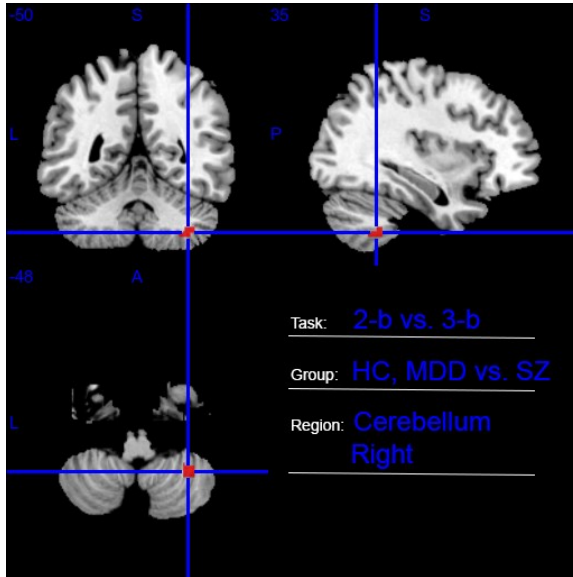**Figure 10:** 2-back vs. 3-back condition



*Figure 10: There is hyper-activation in the cerebellum in SZ compared to HC and MDD when compared a 2-back to a 3-back task.*

## 2.4.4. 3-BACK VS 0-BACK CONDITION

The comparison of a very high demand task to the baseline condition showed a hypo-activation in the right hypothalamus in the MDD group compared to the HC and SZ group. Figure 11 shows the exact location.

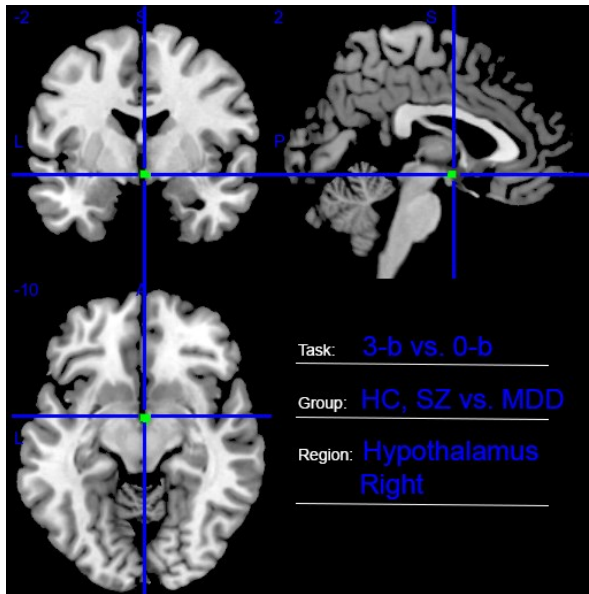**Figure 11:** 3-back vs. 0-back condition



*Figure 11: MDD show in comparison to HC and SZ hypo-activation in the right hypothalamus when compared the 3-back to 0-back task.*

Table 10 summarizes the important areas again and shows the maximum clusters and the maximum contrast in SPM.

**Table 10:** Conjunction analysis of BOLD activity during a n-back task

| Region | Brodmann area | Hemisphere | x | y | z | $k_E$ | Max. |
|---|---|---|---|---|---|---|---|
| **0-back vs. 2-back** | | | | | | | |
| **- MDD, SZ vs HC-** | **46** | | | | | | |
| Inferior Frontal Gyrus | 46 | R | 44 | 44 | 0 | **13** | 2.80 |
| **- HC, MDD vs SZ** | | | | | | | |
| **- Cluster 1 SZ+** | **6** | | | | | **92** | |
| Supplementary Motor Area | 6 | L | -2 | -22 | 52 | | 2.83 |
| Supplementary Motor Area | 6 | L | -2 | -12 | 48 | | 2.64 |
| **- Cluster 2 SZ+** | **6** | | | | | **72** | |
| Paracentral Lobule | 6 | L | -12 | -24 | 76 | | 2.93 |
| Paracentral Lobule | 4 | L | -10 | -26 | 72 | | 2.89 |
| Paracentral Lobule | 4 | L | -10 | -22 | 64 | | 2.75 |
| Paracentral Lobule | 4 | L | -10 | -24 | 60 | | 2.70 |
| **- Cluster 3 SZ+** | **10** | | | | | **39** | |
| Superior Frontal Gyrus | 10 | L | -4 | 58 | 22 | | 2.92 |
| Superior Frontal Gyrus | 10 | L | -6 | 56 | 14 | | 2.77 |
| **- Cluster 4 SZ+** | **39** | | | | | **31** | |
| Supra Marginal Gyrus | 39 | L | -62 | -42 | 38 | | 3.00 |
| **0-back vs. 3-back** | | | | | | | |
| **- HC, MDD vs SZ** | | | | | | | |
| **- Cluster 1 SZ+** | **21** | | | | | **21** | |
| Middle Temporal Gyrus | 21 | L | -56 | -22 | -16 | | 2.74 |
| Middle Temporal Gyrus | 21 | L | -56 | -24 | -12 | | 2.71 |
| **- Cluster 2 SZ+** | **21** | | | | | **17** | |
| Middle Temporal Gyrus | 21 | R | 58 | -16 | -16 | | 2.87 |
| **- Cluster 3 SZ+** | **4** | | | | | **16** | |
| Postcentral Gyrus | 4 | L | -58 | -10 | 46 | | 2.91 |
| **2-back vs. 3-back** | | | | | | | |
| **- HC, MDD vs SZ+** | **-** | | | | | | |
| - Cerebellum Lobule VIIa | - | R | 40 | -48 | -46 | **47** | 3.31 |
| **3-back vs. 0-back** | | | | | | | |
| **- HC, SZ vs MDD-** | **-** | | | | | | |
| Hypothalamus | - | R | 2 | -4 | -10 | **11** | 3.03 |

*Table 10 shows the list of clusters which showed a significant difference in a conjunction analysis in the BOLD signal. The brain region, its corresponding Brodmann area and the side of the hemisphere is shown. The coordinates are listed in the MNI atlas space. The number of clusters kE and the*

*maximum contrast in SPM (Max. SPM (F)) is given. Hyperactivation is marked with a + an hypoactivation is marked with a -.*

# 4. DISCUSSION

## 4.1. BEHAVIORAL DATA

- Hypothesis A could be partially confirmed. The data shows that HC performed best in all tasks, however the results were only significant in two tasks. SZ performed significantly worse in two tasks than HC which is a common result.[131] It is believed that WM deficiency is present independent to the state of illness, but the expression of the impairment is not stable.[132] As our sample consisted of sub-acute patients our findings can be explained and underline the persistent and more severe WM deficiency in SZ. It can also be confirmed that there are changes in the course of the disorder and that, especially in the case of sub-acute condition, not all aspects of WM are equally affected or can be recorded with all tests.

We have hypothesized that MDD perform better than SZ and slightly worse than HC. There was one task were MDD performed significant worse than HC. In all other tasks the performance was not significant worse than HC and always better than SZ. As shown in previous studies WM task performance is more closely related to the state of illness in MDD[133] other than in SZ.[134] There is also a relation between WM performance and the use of antidepressant drugs.[135] Our results can be explained by the fact that the sample consisted of sub-acute patient which favors a good performance on the one hand but on the other most patients received drug treatment which can be a reason for poor performance.

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[131] Zanello et al., 2009

[132] Park et al., 1999

[133] Snyder, 2013

[134] Park & Gooding, 2014

[135] Snyder, 2013

## 4.2. N-BACK DATA

- Hypothesis B could be partially confirmed. As the task is getting more and more difficult the number of correct responses decreases while the response time increases in every group.

There is no significant difference in the 0-back condition neither in accuracy nor in reaction time between groups. This implicates that all individuals were able to perform the task correctly regardless of the associated group. As this was our baseline condition it was crucial that there were no significant differences.

The accuracy of the 2-back task also reflects what we expected. SZ performed significantly worse than HC. This underlines that WM deficiency is a core symptom in SZ patients. MDD performed in between the two other groups with no significant differences to a corresponding group. Suggesting a slightly WM deficiency in MDD, which however, must not be over-interpreted due to the lack of significance in both directions. This suggests that MDD without psychotic symptoms cannot be separated from SZ related to WM performance.

Against our expectations there was no significant difference between the groups in the 3-back task. This cannot be explained by a total exhaustion of the WM capacity because all groups performed better than chance. This result does not show if SZ performed better compared to the other groups in contrast to the 2-back task or vice versa. It shows however that the main WM deficiency in SZ does not lie in the margin areas.

## 4.3. FMRI

- Hypothesis C could be confirmed. The results of our fMRI data reveal alterations between the groups in areas typical for the WM network, including DLPFC, PPC, FP and SMA. The analysis showed especially hyperactivation at the 2-back task which is unique to SZ patients. In the following each area is discussed separately.

### 4.3.1. DLPFC

In the 2-back task hyper-activation was found in the right DLPFC in both patient groups compared to HC, while there were no differences in the 0-, and 3-back task. The expected activation difference between the groups did not occur and SZ had no unique aberration. However, at the same task, the accuracy was significantly worse in SZ, while MDD performed better but still worse than HC. The task was already more difficult for SZ than MDD, suggesting that more of the available WM load was already in demand. In order to keep up the performance, it was necessary to recruit more of the WM network or to alter the strategy. This result goes along with the common belief that if WM load is high, reorganization into higher chunks is needed to keep up the performance. This leads to a higher activation of the lateral prefrontal area.[136] The higher activation in MDD correlates not with a significantly worse performance compared to HC meaning that MDD were able to use the additional resources, while SZ were not able to do so in a similar way. With this result in mind, we can assume that SZ reached their maximum at a difficulty just before the 2-back task, while MDD reached it between the 2- and 3-back task, however earlier than HC. The exhaustion was reached earlier than expected and the 3-back task was more difficult than we assumed. Figure 12 illustrates the present context based on the previous assumptions.

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[136] Owen et al., 2005

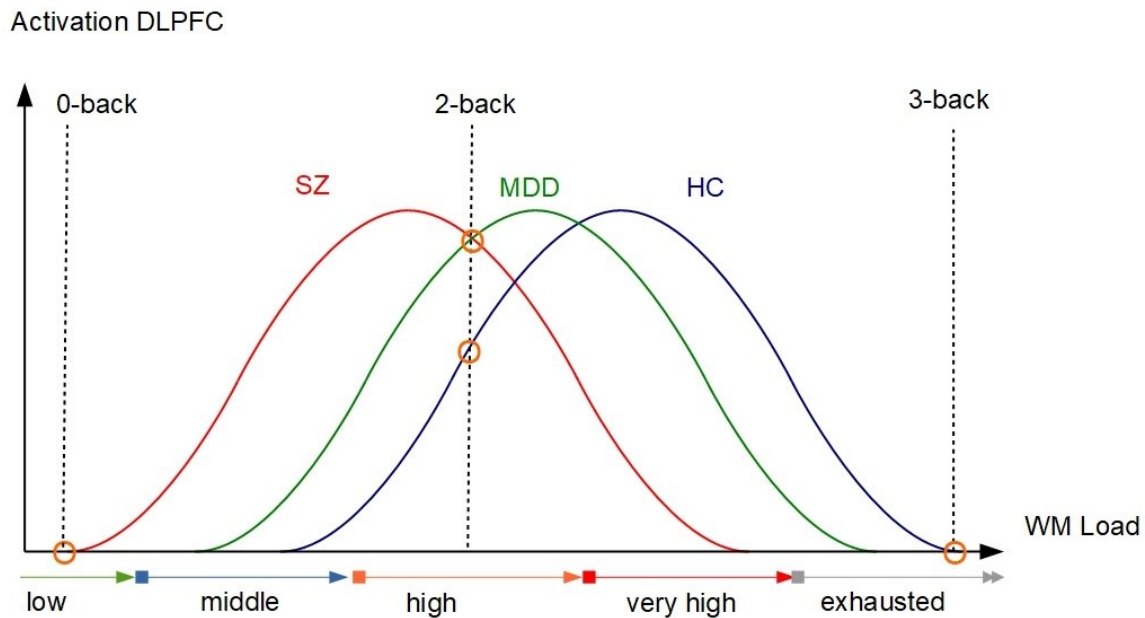**Figure 12:** Activation differences in the DLPFC



*Figure 12 shows the differences in the activation during the n-back task. There were no differences in the 0-, and 3-back task, while SZ and MDD show hyperactivation compared to HC. The results are marked with an orange circle. The shape of the curve is inspired by Monach and the shift is assumed by the performance differences.*

## 4.3.2. FRONTAL POLE/BA 10

The frontal pole, as a key feature to solve more complex tasks with more than one main goal, shows that in SZ patients there seems to be a higher demand in this region in order to solve the task, while MDD and HC could successfully carry out the task with a lower involvement of the area. This shows a deficit in SZ patients to solve more complex task and on the other hand, MDD do not have such a deficit, or at least not to the same extent.

## 4.3.3. SMA (SUPPLEMENTARY MOTOR AREA)

Our findings go in line with current investigations that the SMA is involved in WM-tasks. In the n-back task information must be stored and further proceeded. Here the SMA

seems to play a vital part.[137] As we saw in our investigations SZ had hyperactivation during the 2-back task, implicating that it was more demanding for SZ patient to store the given information and to manipulate it in the further process. Even through the higher demand on resources the performance was worse in SZ compared to the other groups in the investigated task.

### 4.3.4. HYPOTHALAMUS

The hypothalamus is not an area which is typically involved in WM. However, a recent study shows an increase in volume of the left hypothalamus for MDD.[138] We saw in our study a hypoactivation in the right hypothalamus for MDD compared to both other groups, but only when compared the 3- and 0-back task. Our findings underline an alteration of the hypothalamus in MDD.

### 4.3.5. MIDDLE TEMPORAL GYRUS

Even there is currently no evidence that the middle temporal gyrus has a close relationship to WM tasks, there are reasons explaining the hyperactivation in SZ. It could be shown that grey matter in this area is significantly reduced in SZ patients. Furthermore, alterations in this area are connected to hallucinations.[139] [140]Therefore, our finding that SZ patients have a hyperactivation in this area are in line with the current state of knowledge, however the questing remains why this occurs only in the 3-back task.

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[137] Cañas et al., 2018

[138] Schindler et al., 2019

[139] Onitsuka et al., 2004

[140] Zang et al., 2017

## 5. CONCLUSION

The comparison of three groups showed decisive differences not only in the performance but also in the activation pattern of the brain. Especially the link of the WM performance and the activation level of the DLPFC revealed important findings. The expected shift of the u-shaped curve between the three groups had to be adjusted, but the main features could be accepted. We assume that the activation of the DLPFC follows an inverted u-shaped curve dependent on the level of WM load. The turning point is reached in SZ first followed by MDD and HC. However, in easy and overwhelmingly difficult tasks there is no activation difference.

Furthermore, the results underline the predicted WM deficiency in patients with SZ, which goes along with a hyper-activation in brain areas closely related to WM functions. The significant results occurred especially in the 2-back task which is already very demanding. This level of demand seems to be the turning point where the compensation mechanisms are still maintained, but the performance is already significantly decreasing. Especially affected are three regions in the brain, which are crucial for WM, the DLPFC, SMA and frontal pole. Since we have several regions with hyper-activation and no region with a lower activation level in SZ compare to both other groups, we must assume that this is a global dysfunction which is not limited to one area. Of course, this does not answer the question of whether it is a global deterioration in the performance of the individual areas or whether the connections between the areas is changed, so that the demand for each area is higher. Yu, Wu and Wei revealed in their studies different connection deficiencies in similar brain areas in SZ and MDD.[141] [142] [143] Their findings support our results and vice versa. In addition, the descending severity SZ > bipolar disorder > MDD can be confirmed. Of course, there is also the fundamental question what was there first and what is the result of it. This question cannot be answered with our data, but we can say that the

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[141] Yu et al., 2013

[142] Wu et al., 2017

[143] Wie et al., 2018

changes are unique to SZ and make a demarcation to MDD.

On the other hand, patients with MDD have no remarkable deficiencies in WM tasks. The performance is in line with HC. However, there are several tasks where there is no difference in performance. Equally to SZ, the DLPFC shows hyper-activation, but in contrast to SZ the performance was not significantly worse. This leads to the assumption that there is a restricted dysfunction in the DLPFC in MDD, but also that it can be compensated at least partially.

The results reveal two important aspects. The first one is a connection between both disorders. Both groups displayed a DLPFC dysfunction in a WM task. The second one is unique global WM dysfunction which is only found in SZ. These two aspects show that there are similarities as well as differences. While in recent times more overlaps and coherences were found it is also important to investigate in detail the differences between the two disorders.

To gain an even better understanding of the DLPFC and the importance of the brain region a special look is necessary with a working memory task which makes a very precise grading possible between the requirements.

## 6. FUTURE PERSPECTIVE

The goal of medicine is to treat people's disorders so that they can live their life as they know it with no or little limitations because of their disorder. To do this in the best possible way it is crucial to know and understand their disorder. In the case of depression and schizophrenia the diagnosis is based only on clinical symptoms, which is rare in the medical field. The therapy is often difficult, and the results are not satisfying.[144] The question is whether the therapeutic measures are too poor, the diagnosis is in need of improvement or the interindividual differences are too big. In our study we contribute a part to the understanding of the disorders. Further studies should investigate the subcategories of depression and schizophrenia. In this case, it would be important to precisely investigate depressive patients with psychotic symptoms in comparison to SZ and MDD without such symptoms. In our study a WM deficiency with a grading SZ > MDD could be confirmed and now the further question is where bipolar disorder and MDD with psychotic symptoms can be classified.

As shown in previous studies there is an alteration in the network connectivity in MDD and SZ. This knowledge linked to our results arises the question of the origin of the deficiency. Is the hyperactivation a result of a lack in connection or vice versa. Another important question is the alteration in the course of the disorders. Of course, the question of whether there are any changes before the onset of symptoms is particularly interesting. However, answering this question poses great challenges for science and with the answer there are more questions to come. The fundamental question is what the exact mechanisms are underlying the disorders. Step by step science must work in that direction. New methods will bring new insight. Maybe artificial intelligence is the next big step in science and can help answer some questions. Always with the main goal in mind to threat the disorders the best way possible, maybe even before the onset of symptoms.

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[144]  Fava, 2003

## 7. LIMITATIONS

In order to be able to compare groups well, it is important to have as few confounders as possible. Since we had a large sample of patients and control subjects, there was the possibility of achieving a very good matching of the groups. Nevertheless, there are two confounders that need to be described. Those are comorbidities and medication. The truth is that a comorbidity or a psychiatric secondary diagnose is very common in mental disorders and represents majority of a psychiatric disorder. As over 60% of MDD patients in Germany have a secondary psychiatric disorder in the timeframe of one year.[145]

Another issue is the influence of drugs, especially of antipsychotic drugs on working memory. However, it is unacceptable and ethical not justifiable to withhold necessary medications for the sake of scientific reasons.

No patient was in a highly acute phase of the respective disorder. From a humanistic point of view, it would not be tolerable to test patients in an acute state. Also, most patients would not be able to perform on a comparable level. Therefore, the patient's performance under circumstances may differ enormously, to an achievement in a highly acute disorder state. As all patients were in a similar state, so we see no big intergroup differences in this fact, but it is very important to keep it in mind for the interpretation.

We still think our sample is a good representation for each group. We choose carefully the exclusion criteria to have a sample with good comparability and still keep a representative number of patients.

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[145] Jacobi et al., 2014

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