DEFAULT MODE NETWORK
AND ITS ROLE IN MAJOR
DEPRESSIVE DISORDER

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Abstract

This essay investigates the relationship between a malfunctioning Default Mode Network (DMN) and the diagnosis of Major Depressive Disorder (MDD). A deeper understanding of how the DMN affects those brain processes which are implicated in MDD may offer new approaches to reduce the suffering of the very large number of MDD-afflicted patients. The MDD-DMN relationship has been investigated by studying scientific articles within the field of cognitive neuroscience and searching the articles for clues on how a malfunctioning DMN might correlate with the diagnosis of MDD. The essay concludes that there is much experimental evidence in support of there being a strong coupling between a malfunctioning DMN and the diagnosis of MDD.

Keywords: default mode network, major depressive disorder, affective cognition, neuroscience, ACC, PCC.
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**Introduction**

Major depressive disorder (MDD) affects around 15% of the population in the developed world at some point in their lifetime (Heim & Binder, 2012). The disorder is the biggest contributor to the high rates of suicide; MDD and other depressive mood disorders are implicated in 60% of the cases of suicide (Hirschfeld, 2000) The cause of MDD is attributed to several different events and circumstances and several theories and models have been proposed for understanding and treating MDD. Major depression is generally seen as a combination of biological, environmental and psychological factors which are commonly referred to as the biopsychological model (Heim & Binder, 2012). Genes are believed to be the reason for 40% of the diagnoses in the world, meaning that some people are born to be extra vulnerable to the disorder. Episodes of MDD are frequently triggered by an emotionally stressful situation or may be triggered by drug abuse (Heim & Binder, 2012).

Major depressive disorder affects a large spectrum of our different personal functions such as our behavior and our thoughts. The symptoms of major depression range widely, both behaviorally and emotionally. Appetite is often affected by major depression, but the symptoms vary between a heightened and a lowered appetite. This dysregulation of normal behavior is a typical sign of major depressive disorder (Heim & Binder, 2012). Emotional reactions, on the other hand, are not as varied and tend to be more negative in nature. A depressed mood has more negative effects on a person than just their emotional state of mind (Drevets, 2001). The emotions associated with depression are predominantly negative and comprise several common themes such as sadness, anxiousness, restlessness, irritability, anger, and hopelessness. Patients who have remitted from a major depressive episode has a 70% percent risk of developing another episode. (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012)
The human brain comprises a large number of well-identified regions which interact in the neurological processes which shape a person’s perception of himself and his situation and which produces a person’s response in each situation. The interaction of these regions of the brain can be described in terms of how several regions appear to interact in situational-specific networks to process and respond to a given situation. Researchers have identified at least seven networks with distinct patterns of connectivity and function (Yeo, et al., 2011). One such pattern of intrinsic functional connectivity of the brain is the default mode network (DMN) as first elaborated by Marcus Raichle (Raichle et al., 2001).

The default mode network (DMN) is a so-called ‘resting state network’. It is a network of conscious and unconscious control (Raichle et al., 2001). A key characteristic of the DMN is its two-state nature (Spreng & Andrews-Hanna, 2015). The brain areas of the DMN exhibit a reduction of activity during cognitively demanding tasks (in the external world) but exhibit increased activity when persons are at rest (Spreng & Andrews-Hanna, 2015). The DMN is therefore called a ‘resting state network’ while for example, a cognitively active system is referred to as an ‘active network’. When the DMN is active it processes social simulations and helps us reflect on social situations (Spreng & Andrews-Hanna, 2015).

The DMN is importantly involved in the processing of self-focused ruminations in major depressive disorder. These ruminations are more to the effect of having certain thoughts often spring to mind and which are then reflected on. Some of these ruminations can be a positive aspect of a person’s mental life, but if they have a habit of going out of control they could have a detrimental effect. (Raichle et al., 2001). Depression has been shown to have a surprisingly strong connection to these types of rumination (Hamilton J. F., 2015). Studies have shown that persons suffering from major depressive disorder have an especially maladaptive relationship with a limited number of thought-patterns (Greicius, Krasnow, Reiss, & Menon, 2003). When persons become engaged in cognitively demanding tasks, the
DMN system (including the self-referential ruminations) will normally be turned off, but in
persons with depressive disorders, this turn-off does not always take place. If the switch
between focus and mind-wandering gradually ceases to occur, the DMN goes into a state of
disharmony, and the dysfunctional DMN interferes with goal-directed activity, it will give rise
to problems of concentration and to symptoms of major depression (Broyd et al., 2009).

This essay is an investigation into the possible relationship between MDD (Major
Depressive Disorder) and a dysfunctional DMN (Default Mode Network). The aim is to
search scientific articles for insight into models of neuronal functionality and to investigate
whether patients afflicted by MDD also exhibit signs of abnormalities in the switching off of
the DMN when patients change from a resting state to a state of performing cognitively
demanding tasks. Might it, for example, be a contributory cause of MDD when a lingering
DMN-connectivity interferes with the brain’s requirements of focus on a task? Could a DMN-
perspective on MDD serve to increase the understanding of the recurrence aspect of MDD
and are there specific neural correlates between a dysfunctional DMN and the symptoms of
MDD?

To answer these questions, the essay starts with a chapter on major depressive disorder
(MDD) where I deal with the pathophysiology of depression and bring forward the currently
dominating theories of the origin of the diagnosis while also including a more complete
background on the subject. In the following section, Default Mode Network, the investigation
focuses on the default mode network in three separate sub-sections. The first sub-section, the
‘DMN Experiment, covers the experimental background of the early stages of DMN research.
It describes and tests some of the qualities which are now the defining features of the DMN.
Greicius and colleagues present the case for the hypothesis of the resting state network and
elaborate on the connectivity map and adding to the understanding of the involved regions
and their functions (Greicius et al., 2003).
In the experiment, Greicius and colleagues carried out a measurement of the functional connectivity between the PCC and vACC (the two key regions of integration within the DMN), in a sensory non-complex processing task to determine to which extent the activity between the regions correlated. They also performed a visual processing task while monitoring the connectivity maps of the different regions and showed that the maps appeared almost identical to the earlier results when the regions were active. Lastly, in order to get a solid basic understanding of the DMN, they also studied how the involved brain regions acted in a cognitive task (Greicius et al., 2003). Their experiment produced a result which strongly supported the stated hypothesis of the DMN as a resting network (Greicius et al., 2003).

The second and third sub-sections under Default Mode Network focus on the neurological data regarding the DMN. The focus is on the brain regions of the DMN and their respective functions. In the first sub-section under Recurring Major Depressive Disorder and the DMN, the essay focuses on affective cognition which entails brain processes on the border between emotion and cognition and is therefore also strongly connected to both the diagnosis of depression and the processes of the DMN (Broyd et al., 2009).

**Major Depressive Disorder (MDD)**

Major Depressive Disorder is a condition with a wide range of possible symptoms and there are several mechanisms along which MDD can develop. MDD is a state of ‘feeling down’ which has its own spectrum and can range from mild to extreme. Persons who suffer major depressive disorder often notice that the general sense of wellbeing is lacking more than usual and that they tend to avoid some activities and situations more often (Heim & Binder, 2012). The neurological and physical origins of depression are yet to be completely understood. Several theories have been proposed and the framework for understanding and treating depressive disorders is undergoing constant development. One of these theories is the monoamine theory which, has been the dominant theory for a long time and other theories
have appeared with new evidence (Hirschfeld, 2000) (Shyn & Hamilton, 2010). These theories emanate from different points of origin such as; the immune system, the circadian rhythm, an abnormality of the hypothalamic-pituitary-adrenal axis (HPA axis) as well three different structural neurological theories (Shyn & Hamilton, 2010).

Certain personality traits are correlated to a higher risk of suffering a depressive or an anxiety disorder (Kotov, Gamez, Schmidt, & Watson, 2010). Personality traits are measured by several different standards and one of the most common is the big five model. This model lists five different personality traits, which are; Conscientiousness (tendency to be organized have self-disciplined vs spontaneity and carelessness), Openness (being open to new experiences and new thoughts vs never changing behavior and afraid), Agreeableness (compassionate and easy to work with vs competitive behavior and being challenging ), Extraversion (Energetic in social situations vs being alone often and withdrawn), Neuroticism (sensitive and nervous vs confident and secure). Neuroticism in combination having a low score on extraversion and conscientiousness is the personality traits which has the strongest correlation to anxiety and depressive disorders (Kotov et al., 2010). Neuroticism has been correlated with polymorphism, the 5-HTTLPR gene. Patients with this specific change have a higher amount of the earlier mentioned emotional symptoms (Drevets, 2001). Another important trait of neuroticism in regards to its correlation with depression is the typical neurotic response to a stressful situation. The response is more emotionally dramatic than the situation itself. A situation which might be rather ordinary on its own can be interpreted and experienced as a threatening situation, but if only a small frustration is added, then the same situation can be experienced as completely hopeless.

According to the Diagnostics and Statistical Manual of Mental Disorders (DSM-5), (American Psychiatric Association, 2013), there are nine key criteria for what is deemed a major depressive episode. Five of these criteria must have been present during a two-week
period and they must have been a change from earlier behavior as well as either of the criteria (1) or (2) being satisfied. 1. Depressed mood throughout the day, most days. With feelings such as sadness, hopelessness, and emptiness. 2. A loss of pleasure and interest in most or every activity practiced, throughout the day, most days. 3. A significant increase or decrease in weight when not dieting, or an increase or decrease in appetite almost every day. 4. Hypersomnia or insomnia every day, or nearly every day. 5. Psychomotor retardation or agitation close to every day. (This must be observable to others and not solely a subjective observation of slowing down or restlessness.) 6. A loss of energy and fatigue almost every day. 7. Feeling worthless or experiencing excessive guilt nearly every day. 8. Diminished cognitive abilities such having a hard to concentrate or being unable to make decisions almost every day (subjective or observed by others). 9. Thought of death, recurring thoughts of suicide, plans or attempts of committing suicide. Any of these symptoms can cause a significant amount of stress in work, social or in other areas of life. The symptoms are not correlated with the effects of a used substance or any physiological conditions. The episode of major depression is not better explained with any other diagnosis. These criteria for major depressive disorder are only relevant if the patient has not experienced a hypomanic or a manic episode in their lifetime. If they have, the diagnosis of bipolar disorder is more useful.

The diagnosis of major depressive disorder involves a wide array of symptoms. All of which impede a person’s day to day functioning. Emotions reflect the most common symptoms such as low mood, irritability and being unable to experience pleasure (Drevets, 2001). Activities that once gave the patient happiness no longer do and the patient’s behavior changes accordingly. Depression makes the patient lethargic and less active. The patient tends to ruminate which is focusing one’s attention on one’s depressive symptoms and their implications (Marchetti et al., 2012) and issues of low self-esteem are common (Sheline, et al., 2009). Concentration, memory, and cognition are also negatively affected to varying
degrees. The most common type of major depression is the melancholic type which involves the most common emotional effects and can eliminate close to all forms of pleasure in the patient’s life. It is also accompanied by insomnia since the circadian rhythm is also affected (Drevets, 2001).

**Pathophysiology**

The monoamine theory is based on neurotransmitters and the lack of them as the primary reason for major depressive disorder (Hirschfeld, 2000). The theory is divided into different types of disturbances of the neurotransmitters or their accompanying genes. Depletion serotonins precursor (building block) is found to correlate with the diagnosis of depression. This leads to a probable conclusion of there being a lack of serotonin in depression (Shyn & Hamilton, 2010). A second theory is based on the different effects found on noradrenaline in depressed individuals. There is found to be a decreased size of the locus coeruleus located in the pons (Hirschfeld, 2000). This area is vital for the production of noradrenaline which causes arousal. There is also an increase of the alpha-2 adrenergic receptor which inhibits the release of noradrenaline (Ressler & Nemeroff, 2000).

Additionally, there are findings in rats of a decreased activity of adrenergic neurotransmission related to depression. There is evidence of disturbances in the form of polymorphism to the gene coding of the serotonergic receptor, called 5-HTTLPR. There has also been found a similar disturbance of polymorphism to the dopamine receptor. This disturbance causes a decrease in the number of D1 receptor bindings in the striatum, which is linked to major depressive disorder (Ressler & Nemeroff, 2000).

Lastly, there is evidence of an increased activity of monoamine oxidase which is the cause of the degradation of neurotransmitters that has been found in these patients. This combined evidence makes a strong case for the monoamine theory (Bortolato, Chen, & Shih, 2008). Some problematic criticism of the theory are the findings which show no significant
correlation between depression and decreased levels of serotonin and the fact that SSRIs (Selective Serotonin Reuptake Inhibitors) immediately increase monoamine levels in the brain, but they take weeks to show an effect if any at all (Ressler & Nemeroff, 2000).

Selective serotonin–noradrenaline reuptake inhibitors (SNRI) is another type of antidepressant which is closely connected to the earlier mentioned SSRI’s, the difference being the added neurotransmitter noradrenaline reuptake mechanism. There are a number of different SNRI’s out on the market and they are typically used for depression that is treatment resistant to the effect of SSRI’s (Pehrson et al., 2015). There is also coming out other drugs against depression which do not fall into either of these two categories of SSRI/SNRI. One of these antidepressants is Mirtazapine, a NaSSA (Noradrenergic and Specific Serotonergic Antidepressant). It has a mechanism of effect on the alpha-2 adrenergic receptor, on two serotonin receptors 5HT2 and 5HT3, as well on the histamine receptor H1. Mirtazapine has shown a good effect against negative rumination in one study (Komulainen et al., 2015).

There is a significant level of success when using cytokine inhibitors anti-inflammatory drugs against depression (Sutcgil et al., 2007). The most probable reason for this is that depression is often seen in combination with disturbances to the immune system. A common abnormality is a heightened level of cytokines in depressed individuals (Sutcgil et al., 2007). Cytokine is involved in the process of expressed behavior when being sick. There is evidence of a normalization in cytokine levels in successfully treated, previously depressed individuals (Sutcgil et al., 2007). Abnormalities found in the HPA-axis has been correlated with depression due to the gene CRHR1 (Pariante & Lightman, 2008). This gene affects cells involved with stress-hormones and causes their release. It is hypothesized to be a cause of the hippocampal shrinkage in depressed subjects. There is also an increase in response to cortisol in depressed patients, speaking for a role of the HPA axis in major depression (Pariante & Lightman, 2008). Lastly, there is a neurological model which focuses on an increased
response to the salience network, specifically negative emotional salient information (Palaniyappan & Liddle, 2012). While there is also a decrease in the activity of cortical structures involved in regulation of attention. This is hypothesized to cause a negative emotional bias which is common in depression (Palaniyappan & Liddle, 2012). Negative emotional bias is also correlated with impairments of the regions of the DMN.

**Depressive Disorders**

Mood disorders, also known as affective disorders, is a group of conditions where a disturbance in a person's mood is the main underlying feature. Mood disorders can be grouped into the basic groups of elevated mood, depressed mood, and moods which cycle between poles of elevation and depression.

Moods which cycle between poles of elevation and depression, bipolar disorders, are characterized by cycles of abnormal, persistent high mood (mania) and low mood (depression) (Schacter, Gilbert, & Wegner, 2011).

Depressed moods include dysthymic disorders, cyclothymic disorders and major depressive disorder (MDD). MDD, which is covered in a preceding section, is also referred to as major depression, unipolar depression, or clinical depression.

**Bipolar disorder**

Bipolar disorder is a separate type of depressive disorder since it also involves an elevated state such as mania and hypomania which are characterized by elevated, irritable or expansive moods which last for a period of at least one week (Jamison & Ghaemi, 2007). Symptoms include an inflated sense of self-esteem or grandiosity and patients typically need less sleep. The person is more talkative than normal, and his/her thoughts are racing a lot quicker. Attention is easily lost while there may also be an increase in goal-oriented activity (Jamison & Ghaemi, 2007). There might also be an increased involvement in pleasurable
activities such as shopping, sex or gambling. The difference between a hypomanic and a manic episode is that the manic episode is typically more severe in its effects and that a manic episode lasts for a longer time (Jamison & Ghaemi, 2007).

The depressive cycle of a bipolar disorder includes symptoms such as persistent feelings of sadness, being angry or irritable, losing interest and pleasure from activities which were enjoyed earlier. Strong feelings of guilt for no obvious reason, changes in sleep schedule, changes in appetite, feelings of worthlessness and, in the worst cases, thoughts of suicide or committing suicide (Jamison & Ghaemi, 2007). Episodes of bipolar depression are of the same type as episodes of MDD and they follow the same diagnostic criteria. The most common varieties of bipolar disorders are the Bipolar I, the Bipolar II and the Cyclothymic Disorder (Jamison & Ghaemi, 2007). The difference between bipolar I and bipolar II is in the severity of the manic episodes. Bipolar II does not go into a total manic state but stays in the hypomanic episode. Both bipolar I and II also experience depressive episodes. Cyclothymic disorder produces numerous episodes with symptoms of hypomania and depressive episodes which can last up to a year (Jamison & Ghaemi, 2007). The episodes themselves are not strong enough to actually be classified as a hypomanic or a depressive episode, but they share many of the symptoms.

The cause of bipolar disorder is not yet known and there are several theories laid out on the subject. One of these theories is the inflammation hypothesis, which focuses on inflamed cytokines as a reason for the symptoms of bipolar disorder (Goldstein, Kemp, Soczynska, & McIntyre, 2009). Cytokines are proteins which are ejected from a cell and contribute to inflammation. Their involvement is complex in the human brain and they affect glutamate, calcium, and cytokines also are thought to have a role in activating astrocytes and glial cells (Goldstein et al., 2009). There are certain genes which are known for being inflammatory related and bipolar disorder itself is known to be strongly related to genes.
Therefore, there has been some research on polymorphism of the IL1B gene and the IL1RA gene which are inflammation related (Goldstein et al., 2009). In a study with 88 bipolar subjects, a significant increase in the IL1 gene was found in bipolar subjects compared to controls. It was even more common in bipolar persons who had a family history of MDD, bipolar disorder or schizophrenia (Goldstein et al., 2009). This result suggests that there is a link between inflammation and bipolar disorder (Goldstein et al., 2009). Other studies which have focused on using an anti-inflammatory treatment against a certain type of cytokine (PIM), have found no significant results in a reduction of elevated or depressed mood (Goldstein et al., 2009). Leaving the question of the correlation between cytokines and bipolar disorder unclear. It is hypothesized that there might be other kinds of cytokines which have a larger impact on the disorder (Goldstein et al., 2009).

**Seasonal Affective Disorder**

Seasonal Affective Disorder (SAD) is a mood disorder where the individual exhibits a normal, balanced mood throughout most of the year, yet at the same time every year (usually winter) they experience a recurrent depressive episode which matches the symptoms of MDD (Westrin & Lam, 2007). The criteria for seasonal affective disorder specifies that there must be a regular correlation in time when it comes to a major depressive episode in a person with bipolar disorder I or II or in a person with recurrent major depressive disorder (Westrin & Lam, 2007). This correlation in time and the depressive episode is required to occur in a particular season of the year. The depressive episode also has to stop at another time of the year which is constant over several years for the person (Westrin & Lam, 2007). To satisfy the criteria for SAD, there must, in a two-year period, be no other major depressive symptoms except for the episodes related to the particular season. The criteria also require that number of seasonal major depressive episodes throughout the person’s life must be in a substantial majority compared to non-seasonal episodes (Westrin & Lam, 2007).
There are several treatments for seasonal affective disorder, one of these unique to SAD, being the light therapy (Lurie, Gawinski, Pierce, & Rousseau, 2006). Light therapy is based on the concept that during certain seasonal changes, the amount of daylight is decreased, and this might affect the circadian rhythm. This change in rhythm affects aspects of serotonin metabolism which might mediate SAD (Lurie et al., 2006). To help normalize the circadian rhythm there has been research into using artificial light as a replacement for the decrease in sunlight. The light used in light therapy must be of a certain type to successfully simulate sunlight and has shown to be the most effective when delivered in the morning (Lurie et al., 2006). A study done showed that light therapy lasting a week had significant effects on the depressive episode compared to a placebo. Patients have also shown a significant effect in the reduction of depressive symptoms after 8 weeks of antidepressant (Zoloft) usage (Lurie et al., 2006).

**Persistent Depressive Disorder**

Persistent depressive disorder (PDD) is a combination between the diagnoses of ‘Chronic major depressive disorder’ and ‘Dysthymic disorder’. It is stated in DSM-5 that all variations of chronic depression will be classified as PDD (Craighead, Miklowitz, & Craighead, 2013). What makes a depressive episode become chronic is if it continues for two years or more with no symptom-free breaks of more than 2 months. Even though the diagnostic difference between MDD and PDD is only based on the length of episodes, PDD patients have shown a worsening of the symptoms compared to MDD (Craighead et al., 2013). PDD is found to have a larger amount of comorbidity. It has also been found that persistent depressive patients are more prone to suicide than non-chronic MDD patients, and PDD patients also exhibit lower self-esteem and a greater number of depressive cognitive biases (Craighead et al., 2013). For patients with PDD, there was also found to be more numerous instances of PDD in the family (Craighead et al., 2013).
The prognosis over a 10-year period for persons with PDD is a 74% recovery rate, in which the median time of recovery was 52 months. The risk of relapsing into another chronic episode of depression is 71% (Craighead et al., 2013).

There has been a sparse amount of promising research into the causes of PDD and the reports indicate a few promising results in finding a cause (Craighead et al., 2013). Neuroimaging has been successful in bringing forth some differences between patients with MDD and PDD. There has been found a few abnormalities in brain regions between these two diagnoses (Craighead et al., 2013). Patients with chronic depression (PDD) showed signs of a reduced amount of grey matter density in the left temporal cortex as well as atrophy within the right frontal-striatal region when compared to patients of non-chronic MDD (Craighead et al., 2013). PDD has shown a positive effect from the use of SSRIs, a stronger positive effect than its non-chronic counterpart MDD (Craighead et al., 2013). Cognitive behavioral therapy (CBT) which focuses on helping persons in dealing with their depressive thoughts has also shown a positive effect on the group of PDD patients (Craighead et al., 2013). This positive effect of CBT may reflect the fact that cognitive biases, which is a characteristic symptom of PDD, lend themselves well to CBT treatment (Craighead et al., 2013).

**Default Mode Network**

Cognition can be described in terms of regions of the brain which interrelate to perform a task or a function. Such interrelated regions are commonly referred to as networks such as the default mode network, the attention networks, and the executive networks. The default mode network (DMN) is one of the core networks in neuroscience. It is a network of correlated regions in the brain which is activated or deactivated in certain resting and wakeful states. The default mode network is in an active phase when the brain is in an awake, but restful state (Greicius et al., 2003). This happens by default when the focus is not on an active goal-oriented task or of the outside world. Such mental states are mind-wandering and
daydreaming for example (Greicius et al., 2003). During this time a person’s brain is active in reflecting about the individual itself or about others’, as well as focusing on the on the possible future events and accessing older memories. When it comes to the deactivation of the default mode network it is not as straightforward. The deactivation is typically seen in goal-oriented actions in the outside world (Greicius et al., 2003).

The DMN is negatively correlated to attentional networks even though there is a category of goal-oriented tasks that actually do activate regions of the default mode network. In social situations, the social working memory activates the DMN as well as autobiographical tasks (Perrone-Bertolotti et al., 2016). The reason for this activation of the network lies in the nature of reflecting on others, where we usually are trying to understand or contextualize their psychological motivations, thoughts, and emotions. The DMN seems to be a social type of network, among other functions (Spreng & Andrews-Hanna, 2015). The social network’s most important components lie in the ability to understand the feelings and thoughts of other persons. This component is called mentalizing, and its regional network has a correlation to the network of the DMN (Spreng & Andrews-Hanna, 2015). The key regions involved are the temporoparietal junction (TPJ), lateral temporal cortex, posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) and the inferior frontal gyrus. The overlapping regions of these two networks strongly point towards the idea of the DMN having a large impact on our social cognition (Spreng & Andrews-Hanna, 2015). The question asked in neuroscience is of nature to the DMN. Is it the basic function of the DMN to handle the internal social aspects of our daily life?

The default mode network’s nature is the restful state, while the social aspect of our lives is usually not seen as very restful. The DMN is actually highly energy-intensive in its active state (i.e. when the person is at rest). When it comes to the social aspect of it, it seems to be our internal thoughts about our social affairs (Spreng & Andrews-Hanna, 2015). Which
points towards the conclusion that while we are actively experiencing a social situation, the DMN activates and processes it. The mentalizing feature must be active to some degree when the outside world is handing us external information in regards to paying attention to the stimuli itself (Spreng & Andrews-Hanna, 2015).

To be successful in a social situation we are required to mentalize and use reflection to navigate in the social world (Spreng & Andrews-Hanna, 2015). One role of the DMN is to perform a functional integration of important data (external and internal) into an affective experience (Spreng & Andrews-Hanna, 2015). This integration is thought to have the function of creating a sense of personal meaning in social situations.

**DMN Experiment**

The recognition of a DMN has had a catalyzing effect on functional magnetic resonance imaging (fMRI). The use of fMRI has gone from an initial focus on the uprising ‘isolated’ activity of the performance of a certain task, while the brain is in a baseline resting-state, to instead looking at which regions of the brain are active, or even more active, when there is no form of cognitive task occurring (Greicius et al., 2003). The regions which did show activity are the ventral anterior cingulate cortex (vACC) and the posterior cingulate cortex Greicius et al., 2003). These are the unique DMN regions which consistently activate during the baseline state when the brain is in rest. The definition of being in the baseline state (rest) occurs when the participants simply close their eyes and rest. This definition was determined by Raichle and colleagues who used PET-measurements (Positron Emission Tomography) to determine degrees of brain activity (Raichle et al., 2001). Their results lead to the hypothesis that there must be an organized default mode function in the brain that is tied to these correlating regions, the PCC and the vACC (Greicius et al., 2003).
To form these correlating regions and hypotheses into a coherent functioning theory, Greicius and colleagues set out to test the remaining key questions. What they created was the following hypothesis in the form of three questions:

1) If there is such a network as has been theorized from the baseline activity findings (the DMN), then there ought to be more to the connectivity map of these findings. The best way of answering this would be further analysis of the key regions in their resting-state (Greicius et al., 2003).

2) If sensory processing tasks, such as a passive visual processing task, for example, does not lead to a disruption in the activity of the DMN, then this finding must be further investigated.

3) If it is true that the network activity is consistently disrupted during cognitively demanding tasks, then there should be a negative correlation of activity for the regions that are active in the cognitively demanding tasks when the brain is in baseline resting state (Greicius et al., 2003) thereby having a constant anti-correlation to the vACC and PCC.

Anti-correlation meaning that the cognitively demanding task is correlated to turning these regions “off” in the sense of the DMN, and when the cognitively demanding system is itself “off”, the vACC and the PCC function if the DMN is turned “on”. To answer these three questions, Greicius and colleagues only needed a single group of subject that had to perform tasks which involved three different states (cognitive state, sensory-processing and resting) while being examined by the help of fMRI (Greicius et al., 2003).

The cognitively demanding task

The cognitively demanding task (working memory) had the goal of highlighting the regions which exhibited a decrease in activity, as well as the regions which exhibited an increase in activity. The task itself existed of a stimulus (the letter "O") which was shown to
the subjects in 9 separate locations in a 3x3 grid. This was done 16 times then followed with a break of 4 seconds, then followed by another series of the letter "O" in various locations. There were six interchanging experimental and control waves. The difference between the waves depending on it being an experimental or a control wave lie in the subject's instruction. In the control wave, the instruction was to respond if the stimulus appeared in the middle (center) position. While the experimental instruction was to respond if the stimulus appeared in the same position as it had done in the wave that occurred two waves ago (Greicius et al., 2003).

**The sensory (visual) Processing Task**

*The sensory-processing task* (visual processing) was performed in a similar way in which there were 6 cycles of two interchanging waves every 20 s (control and experimental). The instructions were to observe a complex but static black-and-white pattern, with no difference between the groups. The difference was that the black and white colors on the pattern were inverted depending on the group (Greicius et al., 2003).

**The rest task**

*The rest task*, no stimulus, and instructions were to just to close their eyes and try to not think about anything in particular (Greicius et al., 2003).

The aim of the working memory task was looking for activity decline in areas relating to the PCC and the vACC, as well as an increase of activity in the regions of the prefrontal cortex (Greicius et al., 2003). While the aim of the visual processing and the resting state tasks were to build an understanding of the connectivity patterns of the PCC and the vACC, so as to be able to build a connectivity map between the relating areas (Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2008).
Greicius and colleges looked at which other regions correlated with resting-state activity when the task demanding regions were working and this could help them get a better understanding of the other regions seemingly involved in the DMN (Greicius et al., 2003). This was also a key goal of the study; to demonstrate the functional connectivity between regions during the resting state. The results showed a difference in the functional connectivity maps for the two main regions in question (vACC and PCC) (Greicius et al., 2003). The vACC had a strong correlation to the PCC and the MPFC, and the PCC itself had several more matchings of connectivity regions. The PCC has a connectivity map which is close to a complete match with the DMN. It seems that the only two regions that are not implicated by this area are the right amygdala and the left lateral inferior frontal cortex (Greicius et al., 2003). These results mixed with the data showing that there is a strong correlation between decreases of activity in a certain set of overlapping regions when the brain is in a cognitively task-solving mode (Greicius et al., 2003). Added together with the functional connectivity map when the brain is in a resting state, all show strong evidence for a DMN that is activated and deactivated in a reflex-like manner (Greicius et al., 2003).

Regions and Their Involvement.

The PCC-region is heavily involved in memory retrieval, especially episodic memory retrieval. The PCC is a key region of integration for the DMN, being an important component for bottom-up attention in regards to integrating older memories that have stayed relevant, to contextualize the current situation (Raichle et al., 2001). The PCC has been shown to be connected with the medial temporal lobe and is, therefore, a critical structure to the default mode network (Perrone-Bertolotti et al., 2016). Since the DMN is a type of conscious resting state that manipulates memories and builds simulations on top of those memories to help plan the future and to support better decision making (Greicius et al., 2003). What makes the PCC so versatile in this regard is the large connectivity map that the PCC has acquired. One of
these regions is the DLPFC which is involved in the working memory and also has an episodic memory retrieval function (Perrone-Bertolotti et al., 2016). The left ITC is implicated in coordinating our semantic memory and the left PHG, due to its connections to the PCC, is thought to have an important role in the memory retrieval of animals but also in humans (Uddin et al., 2008). The activity maps of the combined regions of the mPFC, the left ITC, the bilateral IPC, the left ITC and the PCC overlap with the processes that are in charge of four different types of memory retrieval, specifically personal facts, non-personal facts, personal memories and non-personal memories (Greicius et al., 2003). The overlap of increased activity in the isolated memory retrieval network and the default mode network seems very well suited to the presumed function of a conscious resting state which is the main function of the DMN (Raichle et al., 2001).

The vACC is of an opposite nature to the higher cortical connections involved with the PCC and its functionality. The vACC is linked to regions such as the nucleus accumbens, the hypothalamus and midbrain and the orbitofrontal cortex which regions are typically involved with certain emotional and autonomic activities within the subcortical and paralimbic regions (Supekar, et al., 2010). What is contributed here from Greicius and colleges is a study base on the two core regions of the DMN, the PCC, and the vACC (Greicius et al., 2003). The opposing nature of these two regions, might also be responsible for the surprisingly large spectrum of varying information sources which are collectively combined and integrated by the network (Spreng & Grady, 2010). Even though each core region of the DNM does have a rather big connectivity map the regions only overlap two of the higher cortical regions, the orbitofrontal cortex and the medial prefrontal cortex (Greicius et al., 2003). The orbitofrontal and the medial prefrontal cortex are important for the integration of emotional stimuli, but also of cognitive information. The PCC and the vACC also overlap with the two subcortical regions of the hypothalamus and the nucleus accumbens (Uddin et al., 2008). The PCC-
connected regions are of a higher cortical nature than the connected regions of the vACC. There are a few important areas where the orbitofrontal cortex and the medial prefrontal cortex overlap and share information and create a more holistic network (Greicius et al., 2003). The existence of such a widely connected network as the DMN will remain the subject of much interesting research and analysis for understanding its many implications.

**Subsystems**

The DMN has several core regions spread over two separate sub-systems. The general default mode network core regions include; the anterior mPFC (amPFC), the bilateral angular gyrus, the lateral temporal lobes, the PCC and the superior frontal gyrus (Perrone-Bertolotti et al., 2016). The core regions of DMN have a correlation of activity between the two separate sub-systems and might function as metaphorical “corpus callosum” between them, helping to transfer information between the two regional sub-systems (Perrone-Bertolotti et al., 2016).

The subsystems of the DMN are called the dorsal medial subsystem and the medial temporal subsystem, both of which are connected to each one of three following key regions; 1) the angular gyrus, 2) the mPFC and 3) the PCC (as well as the precuneus). These key regions have one thing in common in that they all process information regarding the personal self (Perrone-Bertolotti et al., 2016). They are “key-regions” due to their integration of information with the connected regions. The first key region, the angular gyrus is involved in connecting attention, perception and spatial cognition (Andrews-Hanna, Smallwood, & Spreng, 2014).

The second region, medial prefrontal cortex (mPFC) handles a majority of our decision-making and especially the more personal decisions such as decisions regarding how we plan and relate with our families and other people which we acknowledge as ‘family (Andrews-Hanna et al., 2014). The mPFC also processes autobiographical memories which
are fundamental to processing future events and goals (Uddin et al., 2008). The third key region is the posterior cingulate cortex (PCC) which has a large array of functionality to bring to the default mode network. The ventral regions of the PCC are heavily integrated within the network and activate automatically in all tasks connected to the DMN (Andrews-Hanna et al., 2014).

The more dorsal regions of the PCC are involved in the part of our awareness and arousal that we cannot consciously shut off; the involuntary awareness of our surroundings, for example, or the arousal from being pushed when sleeping (Spreng & Grady, 2010). The precuneus which lays superior to the PCC deals with a more basic type of information in the form of incoming; sensorimotor, attentional and visual information. As a whole, the PCC integrates the functions of our involuntary attention to certain things or situations with the information that was contributed by perceptions and older memories. This integration of functions at the same time creates a more unified network. (Andrews-Hanna et al., 2014).

**Dorsal subsystem**

The dorsal medial subsystem of the DMN is one of two subsystems (the second one being the medial temporal subsystem) and is also the subsystem of social reasoning (Spreng & Andrews-Hanna, 2015). The dorsal subsystem is made up of four different regions, each one with a specialization in social understanding. The dorsomedial sub-system is in a stream of communication with the dorsolateral prefrontal regions when we must retain and maintain social data in working memory, as well as when the social task at hand requires executive control (Elliott, Zahn, & Deakin, 2010).

As an integrated entity, the dorsomedial sub-system enables us to use social conceptual knowledge while using theory of mind (reflecting on people’s beliefs and/or thoughts) (Spreng & Andrews-Hanna, 2015). The dorsal medial prefrontal cortex (dmPFC) becomes
involved when we acquire an understanding for someone else’s actions, in the sense of there being an underlying purpose behind the action itself (Spreng & Grady, 2010). The dmPFC allows us to reflect consciously and unconsciously about the purpose of certain choices and behavior in others (Andrews-Hanna et al., 2014). The temporoparietal junction (TPJ) deals with ‘theory of mind’ type of processing which means that it is involved with our understanding of the current beliefs of others (Uddin et al., 2008). The third region of the dorsal subsystem is the anterior temporal pole. It functions by creating an abstract simulation of socially complex situations (Uddin et al., 2008). A sort of conceptual model to give us a simple understanding of socially information-heavy situations. The final region, the lateral temporal cortex, retrieves social semantics to add to the conceptual understandings created by the anterior temporal pole (Andrews-Hanna et al., 2014).

**Medial Temporal Subsystem**

It is now recognized that the medial temporal subsystem performs core functions pertaining to imagination and mental simulation (Spreng & Andrews-Hanna, 2015). This subsystem also has a key role in contextual retrieval, episodic recollection and simulating the individual’s own future. These functions are activated when we either use associative conceptual knowledge to guide our decision-making and/or may be activated when we observe objects that carry strong contextual association (Andrews-Hanna et al., 2014).

An intriguing effect of the function of the medial temporal subsystem is its ability to create what is referred to as a ‘situation model’. In this model, the individual is placed into a certain time, context and place, making the individual capable of navigating in a particular situation which may, or may not, arise (or has arisen). These simulations are often social in their nature due to how the different networks and functions interact (Spreng & Andrews-Hanna, 2015). This interaction, in turn, activates the dorsomedial sub-system due to the mentalizing process it possesses. These sub-systems in interaction (with some additional core-
regions) enables us to develop a functional perspective on a timescale alongside autobiographical memory and social reflection and therefore making prior knowledge relevant to an existing social situation (Spreng & Andrews-Hanna, 2015).

The medial temporal subsystem focuses more specifically on social simulations which are frequently future-oriented and it combines these types of simulations with autobiographical memories (Spreng & Grady, 2010). As with the dorsal medial subsystem, the medial temporal subsystem also comprises four separate sub-regions. The first and most critically needed sub-region of the medial temporal subsystem is the hippocampus. The role of the hippocampus is in remembering the past and trying to imagine the future (Uddin et al., 2008). It is also responsible for the creation of new memories. The second sub-region of the medial temporal subsystem is closely related to the hippocampus and it is the parahippocampus (PHC). Even though the name is similar, the PHC primarily handles recognition and simulations of different spatial sceneries. The retrosplenial cortex (RSC) contributes with its abilities of spatial navigation (Spreng & Andrews-Hanna, 2015). The fourth sub-region of the medial temporal subsystem, the posterior inferior parietal lobe (pIPL), is an integrative region of data from visual, auditory and somatosensory attention and simulation (Uddin et al., 2008).

The function of this sub-region of the default mode network’s is not yet completely understood. The question that arises is if the dorsomedial subsystem of the default mode network is specifically related to our social cognitive processes. And if possible, the whole default mode network might be a specific network for these processes as well. The social narrative comprehension is dependent on several different regions. The dorsomedial subsystem is activated in autobiographical tasks social and these tasks are of a social nature (Spreng & Andrews-Hanna, 2015) If these regions and subsystems don’t function as intended
it can lead to special forms of cognitive biases and emotional problems which makes it easier to develop MDD.

**Major Depression Disorder and the Default Mode Network**

Major depressive disorder and an atypical process of activation and/or deactivation of the DMN have been found to correlate. The self-referential function of the default mode network seems not to work as intended, at least a deviation from the norm has been discovered in depressive patients (Heim & Binder, 2012). The function of self-referential thinking is normally deactivated during external goal-oriented tasks, while it has been shown in major depressive disorder not to deactivate as intended (Sheline, et al., 2009). The DMN is normally a self-referential system, taking the perspective of other people’s beliefs, desires, as well as their possible intentions. This activity of reflecting on others in relation to the self is, at times, presumed to deactivate when attention is devoted to a goal-oriented task. (Perrone-Bertolotti et al., 2016). When attention is directed to a goal-oriented task, this deactivation is no longer as useful, and the function is attenuated. This makes us able to acquire the high state of focus which is required and allows us to lose ourselves in our work (Sheline, et al., 2009). If we can’t shut this flow of activity down, our performance on the goal-oriented task will suffer.

Studies on patients with major depressive disorder show that certain brain circuits which are involved in emotional processing are structurally and functionally abnormal in size and integration of information when compared to healthy subjects (Anticevic et al., 2012). The anterior regions of the default mode network are the dysfunctional regions plaguing the patients (Anticevic et al., 2012). These regions are; the amygdala, the ventromedial prefrontal cortex, the hippocampus and the dorsal medial prefrontal cortex (Anticevic et al., 2012). Sheline and colleagues asked the question whether depressed patients might have the ability to consciously down-regulate their self-referential process (Sheline, et al., 2009) and thereby
possibly gaining control of the negative ruminations. They found that the self-referential processes that are so easily activated in the depressed brain, are more of a general automatic response, which in turn provided the answer to their question that it is not possible for depressed patients to consciously regulate their self-referential activity (Sheline, et al., 2009). Negative ruminative thoughts are a reflective and uncontrollable result of the depressed state itself. The higher the levels of negative ruminations, the higher is the risk of a severe depression (Marchetti et al., 2012). The same rules apply to non-depressed persons. Negative ruminations can occasionally quite accurately predict the onset of different levels of depression.

Negative rumination has been theorized to be a central aspect of major depressive disorder and the DMN is thought to be the central system to this disorder (Anticevic et al., 2012). especially the regions of the ventromedial prefrontal cortex (vmPFC) and the posterior cingulate cortex (PCC). The vmPFC activates when we are making choices of a goal-oriented nature, helping individuals to make their preferential choice. The vmPFC has a key role in our decision-making processes and contributes in guiding us to our preferential outcome (Perrone-Bertolotti et al., 2016).

The PCC becomes activated during episodic memory retrieval and elaboration. Three studies performed by Hamilton and Paul indicated that the general role of the PCC lies in the process of integrating this self-referential data in a spatial-temporal context (Hamilton J. F., 2015). The functions of vmPFC and PCC is partly, but not totally, understood and how the vmPFC and PCC function in relation to the DMN also needs researching further. Hamilton et al propose a slightly different type of view on the DMN. They suggest that another important network complements the DMN, this other network being the salience network (Hamilton J. F., 2015). The salience network, which comprises the regions of the frontoinsular cortex, the amygdala and the dorsal anterior cingulate cortex (ACC), is involved in assessing the
significance of external stimuli. From the combination of these neural networks, the idea that Hamilton and Paul have introduced is that the DMN deactivates not primarily on the directly perceived significance of an external stimulus, but on a valence-ranking of the stimulus which has been internally represented on the basis of input from the salience network. The DMN will respond according to its egocentric evaluation of the valence associated with the stimulus (Hamilton J. F., 2015).

Hamilton and Paul made literature searches of magnetic resonance imaging of the connectivity of the resting-state of the DMN in persons with major depressive disorder. They performed a meta-analysis and compared this connectivity between depressed individuals and persons who had never experienced depression. They found that persons with major depressive disorder had higher functional connectivity between the subgenual prefrontal cortex (sgPFC) and the DMN. Other regions, such as the dorsal ACC, the medial dorsal thalamus (MDT) and the posterior lateral parietal cortex, showed a higher connectivity as well. Another study (Berman et al., 2010) had also found an important correlation between ruminations and a higher connectivity between the DMN and the sgPFC, which supports the findings (Hamilton J. F., 2015). Berman et al went further with the meta-analysis and, using the sgPFC region as a seed region, they found that the sgPFC and the vmPFC exhibited a mutual type of activation pattern in patients with major depressive disorder (Berman et al., 2010). They concluded that this correlation between the regions did predict higher levels of the type of rumination that is significant in depressed patients (Berman et al., 2010).

Hamilton and Paul had also done a study on the correlation between DMN dominance and depressive rumination. Hamilton and Paul divided "rumination" into the two ideas of maladaptive ruminations and reflective ruminations. The type of rumination weighs heavily on the mental health of the subject (Hamilton J. F., 2015). Reflective rumination, for example, has the opposite effect from a maladaptive rumination. Reflective rumination functions
reflexively and is initiated when an ‘alarm’ goes off and promotes a state of focus. Reflective rumination does not have a correlation with MDD (Hamilton J. F., 2015). The other type of ruminations is seen as maladaptive, meaning that they produce a bias towards negative stimuli (Hamilton J. F., 2015).

The result of the data analysis showed that there was no significant difference between the groups as regards the dominance of the DMN (Hamilton J. F., 2015). ‘DMN dominance’ is a term used for the situation when the role of the DMN is more pronounced and stronger than the role of the task-positive network (Uddin et al., 2008). What they did manage to find, however, was that the group with MDD had a higher level of DMN dominance than the control group leading to higher levels of maladaptive ruminations and a decreased frequency of reflective ruminations in the group of MDD patients (Hamilton J. F., 2015).

**Affective Cognition**

Affective cognition could be described as referring to brain processes that take place on the border between emotion and cognition. It can also be described as processing salient emotional data in proper context when we need to cognitively evaluate emotional data to develop an appropriate response (Elliott et al., 2010). The processes of affective cognition are involved in processes such as emotion perception and social and moral reasoning (Elliott et al., 2010). The brain regions involved in affective cognition overlap substantially with DMN-regions which are activated in the restful state. The regions stretch through both the limbic system and the higher cortical regions (Sambatoro, Wolf, Giusti, Vasic, & Wolf, 2013). The limbic system has several intuitively relevant regions for affective cognition such as the striatum, the hippocampus, the amygdala and the insula. Also involved in affective cognition are the higher cortical regions such as the anterior cingulate cortex (ACC), the subgenual cingulate cortex (sgCC), the orbitofrontal cortex (OFC), the medial prefrontal cortex (mPFC) and the lateral PFC (Elliott et al., 2010). One of the leading theories in understanding...
affective cognition is Ochsner’s PFC theory (Sambatoro et al., 2013) which divides affective cognition into two separate systems, the dorsal and the ventral. The dorsal system comprises the dorsal ACC, the hippocampus, and the PFC. The PFC has the more interesting function which is in its controlling of the emotional regulation with the help of a top-down function (Elliott et al., 2010). The PFC is also involved with the ventral system, but in the dorsal system, the PFC handles the reappraisal of contexts in an emotional sense. The ventral system, on the other hand, comprises the amygdala, the ventral striatum, the insula, and the ventral OFC/mPFC, as well as the ventral ACC (Elliott et al., 2010). The differing function of the PFC in the ventral system is fundamental to understanding and visualizing the associations between earlier events and the emotional outcome of the affective processing.

The ventral system holistically deals with bottom-up processing which handles the creation of emotional states, as well as mediating emotional appraising (Elliott et al., 2010). When considering the regions that are involved in the ventral system and its two sub-systems, it is apparent that they have several regions in common with the DMN, both region-wise and, to a certain extent, also function-wise (Sambatoro et al., 2013). The neural correlates of MDD and their associations are important for understanding depression. Their strong associations with the DMN and the areas they share could be a start of a new view when looking at the diagnosis as well as the treatment of MDD (Sambatoro et al., 2013).

The affective-cognitive alterations of MDD are plentiful and involve impaired moral and social reasoning, general cognitive impairment, cognitive biases and a weaker reaction to emotional faces (Enns & Cox, 1997). What is also very interesting is the more specific cognitive symptoms of MDD. Persons with MDD may have a pathological sense of guilt with an increased recollection and sensitivity for negative emotional stimuli (Elliott et al., 2010). All of these symptoms are recognized as cognitive biases and ways of looking at the world which in turn creates an already recognized cognitive schema of depression. It is relevant to
DMN Alterations

Changes in the connectivity of the DMN network are associated with several different mental health issues, one of which is major depressive disorder (MDD). Studies have been able to narrow in on certain alterations in the DMN which have related to different issues and effects. Many of the studies made on MDD have noticed a generally higher level of activation within the DMN. Irrespective of the processes being performed, the activation was higher both during rest and while focused (Grimm et al., 2008). The altered activity was correlated with the anterior part of the DMN involving regions such as ACC and mPFC, but it was also correlated with the posterior regions of the DMN such as the PCC, hippocampus, and parahippocampus. The occurring symptom with this correlation in the DMN is an overlapping spectrum of severity in clinical depressive symptoms (Grimm et al., 2008).

Signs of heightened posterior and anterior DMN activation showed increased levels of hopelessness as well as the severity of depression. One instance of unregulated activity was during emotional face perception (Foland-Ross & Gotlib, 2012). Another similar example of a failure in deactivation is in the viewing and reappraising of pictures of negative emotional nature (Foland-Ross & Gotlib, 2012). Problems with the reappraising of negative pictures were correlated with the ventral and posterior part of the DMN (Foland-Ross & Gotlib, 2012). One important aspect of DMN alterations is the alterations caused to other networks. The reward network, which is also a resting network, is connected to the DMN by the striatum and this relationship is affected in the form of reduced connectivity (Foland-Ross & Gotlib, 2012). This relationship is important to the natural functioning of the DMN because the striatum is involved in cognitive processing and reward feelings. These alterations to the DMN and in

note that all these different processes are also mediated through the default mode network (Sambatoro et al., 2013).
turn the striatum, are likely to give rise to feelings such as a lack of motivation and even anhedonia (Foland-Ross & Gotlib, 2012).

The DMN experiences a general increase in activity even when it should be deactivated during cognitive tasks. Surprisingly, the same symptoms occur in the cognitively demanding, task-positive network (TPN); it requires more resources to be able to function with the interfering DMN (Sambatoro et al., 2013). This means that the DMN is constantly working, reflecting and never resting. While at the same time the cognitively demanding functions must struggle to be able to focus. This situation could be imagined as a problem in transitioning between states with a bias towards the reflecting state (DMN). The most crucial recipe for recurring major depression seems to be a maladaptive, constantly engaging DMN combined with a weak task-related network function (Grimm et al., 2008). This combination of a constantly engaging DMN and a weak task-related network is hypothesized to have an important role in the recurrence of MDD (Sambatoro et al., 2013).

**Cognitive Biases**

The DMN is strongly involved in many of our basic cognitive functions and biases. The strongest cognitive bias in depression and DMN is the cognitive bias of negative emotions. This bias forces our ruminations and reflections towards a negative conclusion irrespective of the situation (Sambatoro et al., 2013). The problems of a negative bias are deeper than just finding yourself having difficulty to see life in a positive light. It’s is hard for the patient to disengage focus from negative stimuli. The patient will generally interpret emotionally neutral information as more hostile and negative than a control group, while also being prone to remember negative information more vividly than the recollection of positive information (Foland-Ross & Gotlib, 2012). The cognitive limitations of this bias take it out of the hands of the depressed patient to consciously dictate or to even notice this ongoing pattern. By the time that these symptoms have developed, the reward system has also been
skewed such that negative stimuli give more feedback to the maladaptive reward system than positive stimuli (Foland-Ross & Gotlib, 2012).

The problematic “recurrence” of recurring depression is categorized as a type of cognitive bias. Even though there are successful pharmacological and psychological treatments of MDD in the short term (Marchetti et al., 2012), the problem lies in the long-term treatment, which has proven difficult to accomplish. MDD is more easily triggered than treated. Studies have shown a 70% recurrence of symptoms (Marchetti et al., 2012). An added difficulty in treating MDD is the fact that for every time a new depressive episode does arise, it makes the recurrence statistic of 70% go up (Marchetti et al., 2012) such that for each episode there is an increase in the probability of yet other, future, episodes. This is expressed in how easily it is triggered. After having experienced several depressive episodes, the difference is that, whereas previously a strong stressor was required to trigger an episode, now also minor stressors qualify for setting an episode off (Marchetti et al., 2012). To be able to treat this increased sensitivity and to create more efficient treatments for depression, it is important to understand depression on a neural scale (Marchetti et al., 2012).

The neural scale is becoming increasingly better understood in depression research. Research using MRI imaging techniques has added significantly to the understanding of the field of the neural correlates in regards to general depression (Marchetti et al., 2012). With the help of MRI, techniques researchers have discovered neural circuitry in charge of the attention-emotion interactions. These neural circuits have been shown to be a key component in the pathophysiology of depression (Andrews-Hanna et al., 2014). There is evidence pointing to a faulty top-down control system which means that the higher cortical structures do not always correctly regulate the lower cortical activity. The higher cortical structures, in this case, are the prefrontal regions, while the lower cortical regions are the limbic system (Andrews-Hanna et al., 2014). Amongst these different regions, the ACC (anterior cingulate
cortex) has been shown to be very important to the functioning of both the higher and the lower regions (Andrews-Hanna et al., 2014).

To understand the importance of the ACC, it is important to be aware of its two fundamental roles in enabling neural circuitry to function (Andrews-Hanna et al., 2014). The ACC monitors conflicting signals and handles the response selection (dorsal), and the ACC’s ventral region helps to process emotion-related signals (Andrews-Hanna et al., 2014). The dorsolateral prefrontal cortex (DLPFC) has the ability to select the area where the attention is focused, or how attention is distributed throughout the system, and the ACC can signal to this area to alter its focus (Andrews-Hanna et al., 2014). Altering the focus of attention can have domino-like consequences and may affect the amygdala’s emotional processing (Marchetti et al., 2012). If this emotional processing is inhibited it can cause disruptions within the very neural circuitry whose role it is to handle emotion processing tasks (Anticevic et al., 2012). A disruption of these processes has been correlated to depression, and the side effects of such disruptions do resemble several of the information processing problems that tend to occur in patients with depression (Andrews-Hanna et al., 2014). The attentional problems in depression are strongly dependent on how attention is allocated. The cognitive alterations influence where, and how, our resources are used, making it a lot harder to remove focus from negative stimuli to more task-relevant or at least positive stimuli. It is a failure of the cognitive control over the attention that is causing many of the issues (Anticevic et al., 2012). Stressful situations seem to make this attention-allocating problem even more pronounced which in turn promotes more ruminations. Here the imaging techniques have contributed to discovering a correlation between DLPFC-activity and the experiencing of difficulties in directing attention away from negativity (Andrews-Hanna et al., 2014).

The increased probability of recurring depression with each new depressive episode has been linked to the ACC (Andrews-Hanna et al., 2014). Impairments of cognition
associated with the ACC seem not only to increase with every new depressive episode, but also to persist when recovery has been accomplished (Andrews-Hanna et al., 2014). This shows that the ACC-region might be a key component in developing a treatment for the increase in recurrence-probability with each new episode of MDD. Not having proper cognitive control over attention seems to have an increasingly large role in the diagnosis of depression (Marchetti et al., 2012).

**Pharmacological Options Against Rumination and Cognitive Bias.**

There are two different monoamine-based drugs which have shown an effect on the increased self-focus which is present in depression. These two are; Mirtazapine (NaSSA) and Reboxetine (SNRI). The self-referential emotional processing has started to take a larger role in the psychopathology of depression in recent years. So has the focus point of the drugs which are used against it (antidepressant), more research has been reported on antidepressants’ potential of affecting these functions in the brain. The SNRI “Reboxetine” and especially the more unique drug “Mirtazapine” has shown a significant effect on these regions and pathologies, such as the cognitive bias towards negative emotional stimuli (Komulainen et al., 2015).

In one study made by Komulainen and colleagues, they showed a significant effect on the self-referential emotional system after one single dose of mirtazapine. This drug has an effect on a large variety of different receptors including; 5HT2, 5HT3, H1 and on the alpha-2 adrenergic receptor (Komulainen et al., 2015). The drug has shown an effect on the cortical midline structures (CMS) by decreasing the general response within these regions. This includes areas such as the ACC, PCC and the MPFC, areas which are highly involved in the DMN and in cognitive biases. The decreased activity contributes to a down-regulation of the self-referential processes of the depressed patient. This is hypothesized to lead to less rumination as well as a downgrading of the negative self-focus for the depressed patient
(Komulainen et al., 2015). Studies on Reboxetine, an SNRI, shows that repeated dosage leads to a heightened sensitivity to positive self-referential words, but no decrease in activity to negative stimuli (Di Simplicio, Norbury, & Harmer, 2011). The difference between Mirtazapine and Reboxetine is that whereas Reboxetine reached an effective level within a week but is only effective for heightening the sensitivity towards positive stimuli, Mirtazapine showed significant effect within a time of two hours and effects also the activity of negative stimuli. (Komulainen et al., 2015). As a drug to help against the symptom of disrupted cognitive function from depression, mirtazapine would be the preferable drug according to these results.

**Discussion**

This essay is the result of a study of the relationship between a dysfunctional DMN and the diagnosis of MDD. The concept of a resting state DMN is reviewed in terms of its functionality and of the regions of the human brain which comprise the network.

This research into the DMN and its relationship to MDD is a new and might lead to novel methods for treating MDD and for understanding MDD from a complementary perspective. The research in this essay is also relevant for gaining a better understanding of the functionality of the DMN and its implications on cognition and mental health.

The essay has been made as a literature study. It was done using Google Scholar and PubMed. Search criteria for articles included the terms of MDD, DMN and affective cognition and variations and combinations of these terms. The search resulted in over 25 scientific articles with relevant information on the subject of DMN and MDD.

An initial section of this essay describes depression and focuses on the dominant manifestations of depressions as well as the pathophysiology of depression. That section serves as background to the complementary, DMN-centered view of MDD and illustrates the
potential of the DMN-perspective to contribute to the understanding of MDD and to possibly offer novel approaches to the treatment of MDD.

In two following sections, the focus is on the DMN and its neurological regions and functional features. Even though the DMN is called a resting state network it is, when active, involved in performing in much, highly complex neurological processing and it is one of the more resource-demanding networks of the brain. If the DMN does not deactivate properly in favor of cognitive processing, it continues to use large amounts of resources (Perrone-Bertolotti et al., 2016). In such a state, the DMN is constantly reflecting and creating simulations, in which case the cognitively demanding task network appears to remain partly suspended. Since, due to the conflict of resources, neither network can function as intended (Sambatoro et al., 2013), it is believed that this state of partial limbo may be a key contributor to the development of depressive disorders.

The information in the sections on DMN alterations and cognitive biases support the assumption of the aim of this essay, that the symptoms of MDD correlate to the symptoms of a dysfunctional DMN. It has been shown that changes in the network are associated with MDD and that patients with MDD have a DMN which is more often activated than for control subjects. The activity is higher both during rest and while concentrating. This increase in activity for patients with MDD was seen in both the anterior and posterior of the DMN, the larger the increase, the stronger was the severity in clinical depressive symptoms (Grimm et al., 2008).

The complementary aim of this essay, to determine whether the recurrence aspects of MDD have any connection to the functioning of the DMN, is supported by the finding of increased probability of recurring depression when the ACC functions abnormally and the lasting damage that is sustained after periods of abnormal behavior. The weakening of the
ACC after episodes of abnormality appears to make it easier for patients to fall back into an episode of major depression (Marchetti et al., 2012). The ACC is a key region in the DMN, which makes the case that if the DMN is dysfunctioning, the ACC is at a large risk of dysfunction as well. When this happens, the probability of having a recurring episode of major depression increases, both in the present instance of dysfunctionality and in the future (Andrews-Hanna et al., 2014; Marchetti et al., 2012).

The studies referenced in the sections on DMN alterations and cognitive biases lend support to the question in the aim of this essay regarding whether there are specific neural correlates between a dysfunctional DMN and the symptoms of major depressive disorder (MDD). A key common region is the ACC whose importance both in MDD and in the DMN is attributable to its vast interconnectivity and to the range of important functions performed. The second region with relations to both the DMN and MDD is the DLPFC. The function of this region in the DMN is allocating attention away from negativity. A dysfunctioning of the DLPFC is found to correlate to difficulty in drawing attention away from negativity, and therefore increasing the risk of negative biases which are often found in MDD (Andrews-Hanna et al., 2014).

It appears that the DMN is sensitive to interruptions that might put it out of balance (Marchetti et al., 2012). When the DMN gets put out of balance, the whole network suffers an increased risk of collapse (Marchetti et al., 2012). The research on the lasting effects of disharmony of the ACC by Marchetti and colleagues illustrates the role which triggers events and circumstances can have on the development of depression and illustrates why subjects do not have the same sensitivity to developing depression (Marchetti et al., 2012). It can be theorized that the lower an individual’s threshold of triggering a depression, the faster the treatment needs to arrive. An impairment of a key DMN-region such as the ACC increases the probability that an interruption will develop into a widespread disruption.
Other studies and research show a strong relationship between a malfunctioning DMN and the affliction of MDD. One of these studies by Sheline and colleagues concluded that the reduction of DMN-activity when viewing and reappraising negative images was weaker in depressed patients compared to non-depressed control subjects (Sheline et al., 2009). The results of this particular study suggest that the DMN is in a state of increased activity and also fails to down-regulate its activity in depressed patients (Sheline et al., 2009). Another study by Hamilton and colleagues which looked at adaptive and maladaptive ruminations connected to the DMN and MDD, concluded that MDD participant exhibited an elevated amount of DMN dominance and higher levels of depressive, maladaptive rumination compared to non-diagnosed subjects (Hamilton et al., 2011). The MDD participants also exhibited lower levels of adaptive, reflective rumination than the controls (Hamilton et al., 2011).

The number of scientific articles on the relationship between mental disorder and the DMN is quite large. A systematic review of empirical studies (Broyd, et al., 2009) identifies twenty-six findings of altered DMN activity in individuals with mental disorders. Of these twenty-six studies, however, only one study was categorized under the mental disorders subheading of depression (Greicius, et al., 2007). This study confirms that abnormalities in the resting state functional connectivity of the DMN regions were significantly greater in depressed subjects compared to controls. The fact that only one study of twenty-six focused on the relationship between altered DMN and MDD, suggests that more insight into MDD could be gained from further research into MDD’s relation to abnormalities in the DMN.

An increased activation of the DMN is referred to as a “maladaptive DMN”. A maladaptive DMN which is constantly working and reflecting/daydreaming leads to attention-focusing conflicts since the DMN should normally deactivate when a cognitively demanding task requires attention (Sambatoro et al., 2013). Although the DMN is a resting state network, it uses quite much energy and a maladaptive DMN leads to a struggle of resources between
focusing and ruminating. This struggle may eventually lead to a state of mental exhaustion. These symptoms of excessive daydreaming, problems of concentration and mental exhaustion are well-recognized symptoms of MDD (DSM-5) (American Psychiatric Association [APA], 2013),

Another significant result from the research for this essay is that DMN and MDD are closely associated with cognitive biases. A cognitive bias of focusing on negative emotions is a frequent symptom of MDD. The DMN is found to be highly involved in the makings of these negative ruminations. This is a further connection between MDD and DMN (Sambatoro et al., 2013).

Limitations.

Most of the scientific articles researched for this essay were published more than five years ago. Newer research and research results not available online might offer alternative interpretations of the DMN-centered view on the affliction of MDD.

Another limitation to this study is that since the DMN comprises several important brain regions, it is sometimes not possible to isolate individual correlations between brain areas and networks which are frequently engaged in several, simultaneously ongoing and parallel processes.

The only malfunction of the DMN considered in this study is that of the DMN failing to deactivate and the residual activity interfering with the resources required to execute cognitive tasks. There may be other malfunctions of the DMN which also correlate with the symptoms of MDD.

Further research is required to develop the scientific understanding of the DMN and its relationship to MDD. One key area for further research is the central role of those processes of the ACC which impact on the DMN and on the symptoms of MDD. A deeper
understanding of those brain processes will be instrumental in developing the next generation of treatment plans for MDD patients.

**Conclusion**

The literature researched for this essay supports the contention that a malfunctioning DMN is importantly related to MDD. Experimental studies show conclusive links between abnormal DMN activation and symptoms of MDD. The conflicting demands on brain resources which follow when the DMN fails to deactivate are found to contribute to episodes of MDD and to the recurrence aspect of MDD.

**References**


