Degree project

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Healing the Wandering Mind: Treatment of the Default Mode Network in Major Depressive Disorder

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Abstract

Rumination, or extensive mind wandering defines one of the key cognitive symptoms of major depressive disorder (MDD). Several symptoms included in the psychiatric disorder have been associated with altered connectivity within the large-scaled system default mode network (DMN). Although it's well-known that antidepressant treatment, such as selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) tend to positively affect symptoms and alterations of MDD, results are inconsistent regarding DMN connectivity pre-and-post treatment. This systematic review aims to compile findings from studies investigating DMN connectivity in MDD patients' pre-and post SSRI and SNRI treatment, and to find possible correlations with symptomatic improvements. Five articles were included for further analysis after the literature search in MEDLINE ESBSCO and Scopus. Main findings are in alignment with previous research and suggest both hypo-and hyper DMN connectivity at baseline in MDD patients, and connectivity patterns significantly similar to healthy controls following antidepressant treatment. Future research might consider placebo controlled trials for more diverse, and quantified results, and also consider further investigation on both first-line treatments and other promising antidepressants.

Keywords: the default mode network, functional connectivity, major depressive disorder, antidepressant treatment.

Healing the Wandering Mind: Treatment of the Default Mode Network in Major Depressive Disorder

The default mode network (DMN) was coined in a functional magnetic resonance (fMRI) study more than 20 years ago by Professor Marcus E. Raichle, and his colleagues (Raichle et al., 2001). Their aim was to define neural activity for a set of interconnected brain regions hypothesized to have an ongoing intrinsic activity during resting-state condition. The ongoing activity was suggested to increase during mind wandering (e.g., the mind wanders away from current activity), and decrease during goal-directed behaviors (i.e., when attention is focused on cognitively demanding tasks).

In the early 90s', Professor Raichle started noticing activity decreases in control subjects resting quietly with their eyes closed. This observation was rarely observed at the time, unlike task-induced activity increases (Raichle, 2016). Moreover, that active process was suspected to be modified with a particular task (Gusnard & Raichle 2001). Sequentially, resting control states were included in many ongoing experiments. Further, by reversing the subtraction process, meaning subtracting control state data with experimental data, it was possible to observe control state data. It became clear that regardless of the task under investigation, activity decreases continually occurred, particularly in the posterior cingulate cortex/adjacent precuneus. Later that decade, a meta-analysis was conducted to observe potential regions of the brain's attention network (Shulman et al., 1997). In addition, the study found a set of brain regions exhibiting task-induced reduction, with posterior cingulate cortex/adjacent precuneus as the most prominent components.

Consequently, this observation led to the seminal study of the DMN, "A default mode of brain function", that comprised not only posterior cingulate cortex/adjacent precuneus, but also regions within medial prefrontal cortex, sub regions of the anterior cingulate and orbitofrontal cortex and medial, lateral and inferior areas of parietal cortex. Today, there is a major interest in the brain's intrinsic ongoing activity, in particular the DMN in disease, such as mental disorders (Raichle, 2016).

Mind Wandering and Major Depressive Disorder

Mind wandering is a core aspect of human cognition, but the experience can be associated with a significant cost, including poor psychological well-being (Andrews-Hanna, 2014). Rumination (i.e., extensive mind wandering) is a subtype of mind wandering, defined as a tendency related to the self, with a repeated focus on symptoms of distress, and its causes and consequences.

Rumination characterizes the cognitive key symptom of major depressive disorder (MDD), which is a common (20.6% lifetime prevalence in adolescents; Hasin et al., 2018) and severe psychiatric disorder that constitute the leading cause of disability worldwide (World Health Organization, 2008). MDD comprises a complex set of symptoms, such as depressed mood, loss of interest in previously rewarding activities, weight loss or weight gain, insomnia or hypersomnia, psychomotor aggregation or retardation, fatigue, sense of guilt, impaired ability think in social and ethical aspects, and suicidal thoughts or attempts. These are symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013).

Severity is an important characteristic in MDD, and can be measured by various, reliable scales. The Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) and Beck Depression Inventory (Beck, Steer & Brown 1996) are widely used scales with high reliability and validity. HAMD-17 is based on scores, which further categorize depression severity into non-depressed (0-7), mildly depressed (8-16), moderately depressed (17-23) and severely depressed (>24, up to 52). The inventory by Beck and colleagues is a self-scored 21-symptoms scale, which reflects the intensity of clinical symptoms, but also depressive ideation in the normal population (each symptom receives a rating of zero to three, with cut-off scores 1-10 normal, 11-16 mild, 17-20 borderline clinical depression, 21-30 moderate, 31-40 sever, and over 40 extreme depression).

Subsystems of the Default Mode Network

Dysregulation of information processing in attention, memory and prospection are symptoms of MDD, but also functions mediated by the DMN (Sambataro et al., 2013). Although DMN connectivity tends to oscillate in synchrony, regions can be divided into different subsystems, each implicated in various cognitive processes (Andrews-Hanna et al., 2010; Buckner et al., 2008).

One of the most commonly used subdivision comprises the core subsystem, and subsystems including anterior, posterior, and ventral regions. The core, i.e., anterior medial prefrontal cortex and posterior cingulate cortex, links all subsystems together (Buckner et al., 2008), and is implicated in self-referential cognition (e.g., recalling memories), cognition, mentalizing (i.e., understanding mental states of oneself or others), autobiographical memory, and moral decision making (Andrews-Hanna et al., 2010). Regions of the anterior subsystem, i.e., dorsal medial prefrontal cortex, temporal poles, lateral temporal cortex, and temporoparietal junction (Buckner et al., 2008), respond to activities such as mentalizing, moral decisions, social reasoning, and conceptual processing (Andrews-Hanna et al., 2010). The posterior subsystem, i.e., bilateral precuneus, (Li et al., 2013), is implicated in visual

processing, motor planning, cognitive processes, retrieving memories, and self-generated and internal mentation (Sambataro et al., 2013). Finally, regions within the ventral subsystem of the DMN, i.e., hippocampal formation, retrosplenial cortex, and inferior parietal lobule, respond to episodic and autobiographical memory, navigation and imagery of memory-based simulations (Andrews-Hanna et al., 2010).

The Default Mode Network in Major Depressive Disorder

The functional organization of the DMN comprise anatomically distinct brain regions which activity is thought to be highly-synchronized at rest, i.e., *resting-state functional connectivity* (Biswal et al., 1995; Greicius et al., 2003; Zhang and Raichle 2010). Spontaneous activity, that is activity not related to a specific task, can be observed by resting-state fMRI, further thought to reflect mental states such as mind wandering (Buckner & Krienen 2013; Fox and Raichle 2007; Shirer et al., 2012). Resting-state fMRI studies have for the past decades frequently reported alterations on resting-state DMN connectivity, among other large-scale systems, in association to several neurological and psychiatric disorders (Anand et al., 2005; Bergouignan et al., 2008; Bluhm et al., 2009; Greicius et al., 2007; Grimm et al., 2009, 2011; Hamilton et al., 2011; Sambataro et al. 2013; Sheline et al., 2010; Zhu et al., 2012).

Studies suggest the DMN to play a central role in the underlying structural and functional abnormalities of MDD (Kaiser, Andrews-Hanna, Wager & Pizzagalli, 2015). Studies have reported hypo connectivity, i.e., loss of structure or decreased connectivity between brain regions, as well as hyper connectivity, i.e., excessive connectivity between brain regions, within the DMN in MDD patients. In turn, these functional connectivity alterations are leading to reduced flexibility for the brain to function properly.

Seminal work on resting-state DMN connectivity in MDD patients have observed hyper connectivity during exposure of negative emotional stimuli (in comparison to healthy subjects), particularly in the subgenual anterior cingulate (Greicius et al., 2007). The subgenual anterior cingulate plays an important role in emotional regulation, known to be dysregulated in MDD patients (Bluhm et al., 2009; Grimm et al., 2009). However, studies have also observed hypo connectivity in subgenual anterior cingulate, following antidepressant treatment (Bora et al., 2012; Du et al., 2012; Drevets, Bogers & Raichle, 2002; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Also, increased connectivity have been found in DMN's posterior regions, including posterior cingulate cortex (PCC)/adjacent precuneus and amygdala (Sambataro et al., 2013), and in the ventral region of the DMN in the hippocampal formation and parahippocampus (Du et al., 2012; Peng et al., 2015; Ritchey et al., 2011; Lee et al., 2011). Moreover, increased connectivity between ventral and anterior subsystems of the DMN have been observed in MDD patients (Hamilton et al., 2012). Interestingly, all previously

mentioned alterations are suggested to be positively correlated with the length of current depressive episodes as well as with depression severity (Greicius et al., 2007; Hamilton et al., 2011).

Treatment of Major Depressive Disorder

SSRIs and SNRIs antidepressants are first-line treatment for MDD patients (Hirschfield, 2012). These antidepressants inhibits the uptake of monoaminergic neurotransmitters and thereby increasing their synaptic availability. SSRI inhibits the reuptake of selective-serotonin, and SNRI inhibits serotonin- norepinephrine reuptake. Subsystems within the large-scaled network are suggested to be differently affected by antidepressant medication because of their heterogeneity in function (Buckner, Andrews-Hanna & Schacter 2008).

Studies that are investigating in SSRIs antidepressant effect have reported significant decreased connectivity in the occipital cortex (Cheng et al., 2016). On the other hand, SSRI treatment have been reported to increase functional connectivity within the DMN, in particular dorsolateral and dorsal medial PFC, and middle cingulate cortex bilaterally. Other studies proposes antidepressant treatment to normalize network abnormalities in MDD suggested in dorsal medial, dorsolateral and ventral lateral PFC among other regions (Bluhm et al., 2009; Grimm et al., 2009; Posner et al., 2013; Sheline et al., 2001). This antidepressant effect is known as the “normalization hypothesis”.

Aim of Thesis

In summary, researchers in this field have come to many conclusions. Although, we still need to answer how SSRIs and SNRIs, as first-line antidepressants are affecting resting-state functional connectivity of the DMN in MDD patients. Studies suggest the DMN as an important network in understanding the underlying mechanisms of MDD. Especially relevant is that large evidence suggests SSRIs and SNRIs to modulate altered resting-state connectivity in MDD patients. However, results are inconsistent due to the complexity of MDD symptoms and widespread network abnormalities seen in this condition. By further investigation on treatments' effects we can deepen our understanding of the underlying mechanisms of MDD and provide better, and more personalized treatments. Therefore, this systematic review aims to address the current issue of result heterogeneity, and therefore systematically review articles that are investigating resting-state DMN connectivity in adult patients with MDD pre-and post SSRI and SNRI antidepressant treatment.

Methods

Search Strategy

The author conducted the literature search on March 7th in the databases MEDLINE EBSCO and Scopus. Only English articles were reviewed with a year limit restricted from 2001 (with reason due to the seminal publication on the DMN). The search string used: (default mode network) AND (major depressive disorder OR depression OR MDD) AND (therapy OR treatment OR antidepressants) AND (fMRI OR functional magnetic resonance imaging). The initial search gave 566 search results (i.e. MEDLINE EBSCO n= 175 and Scopus n=367). After removing duplicates (n=175), 391 articles were acquired. 375 records were excluded based on inaccurate title, no interest of experimental group, lack of control group, or control group engaged in cognitive activity other than resting-state condition, or lack of data. After reading full-text articles (n=15), 10 were excluded based on no participants group of interest (n=1), no control group of interest (n=1), no exposure of interest other than resting-state (n=3), and no outcome of interest (n=5). Finally, 5 articles met the inclusion criteria for the qualitative synthesis (see Figure 1 illustrating the search process overview in a PRISMA flow chart).

Inclusion and Exclusion Criteria

Peer-reviewed articles written in English were included if resting-state fMRI were used. Participants included are 1) adults over age of 18 2) patients with MDD diagnosis based on DSM-IV criteria 3) currently not taking any antidepressant medication. The articles must investigate 1) SSRI or SNRI antidepressant treatment with respect to healthy control subjects 2) assess depression scores pre-and post-treatment using Hamilton Depression Rating Scale (Hamilton, 1960). Studies were excluded if participants had any comorbidity disorder in Axis I or II (other than major depressive disorder), or if cognitive exposure were the only fMRI design. Studies using single-dose treatment, or SSRI or SNRI in combination with psychotherapy were also excluded whether not results are reported separately.

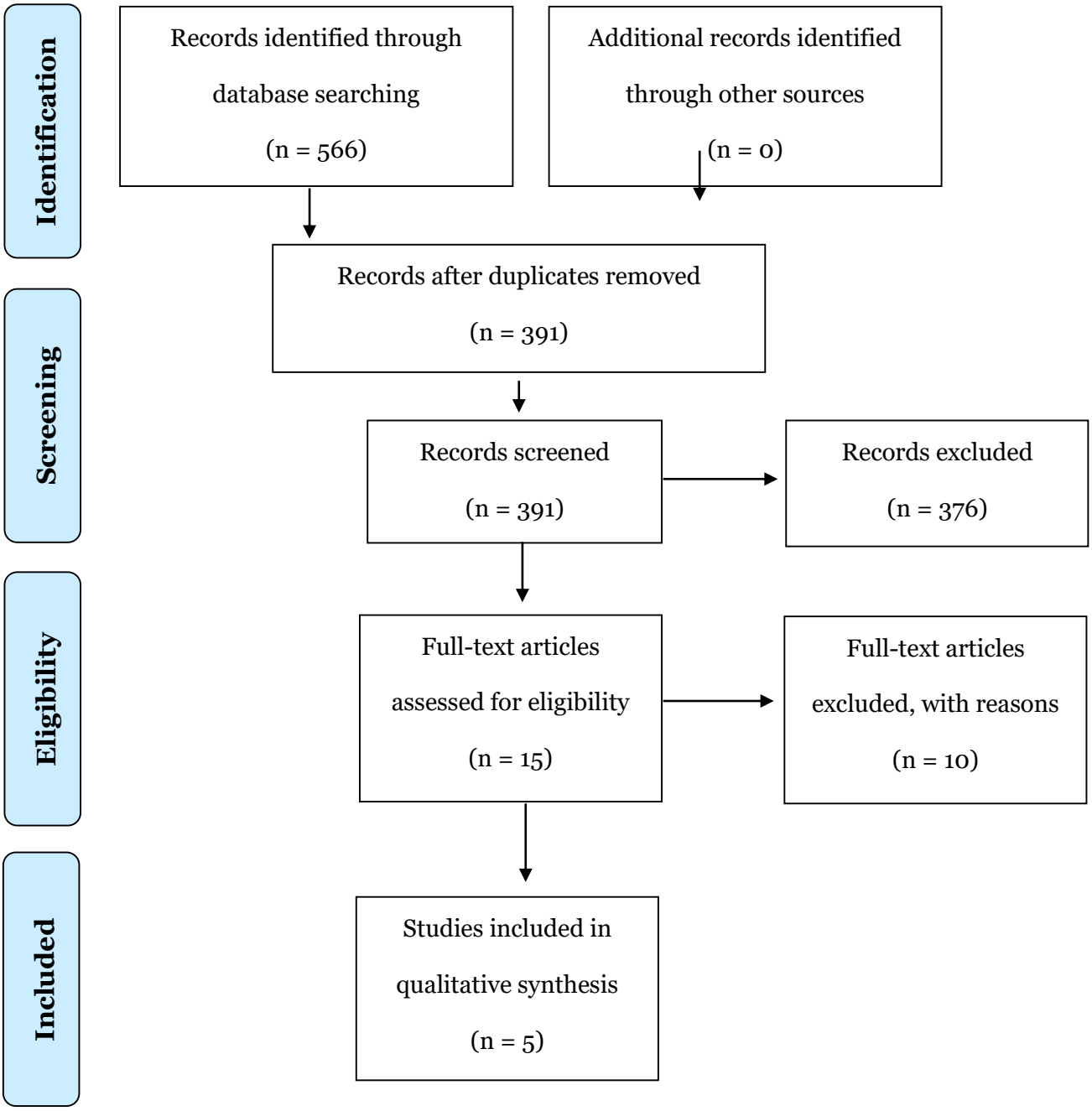
Data Extraction

The data will be summarized in a table, in accordance with the PICO criteria. Information of interest are the author, and key references. Data regarding participants' mean age, gender, and sample size will be extracted to identify possible differences, hence influencing the reliability of the results. Measures of resting-state fMRI and HAMD-17 (scores 17 and above) at baseline, and post-treatment in order to link DMN connectivity with illness severity is of interest. Type of treatment, i.e., SSRI or SNRI, and treatment period is of interest to identify results of altered resting-state functional connectivity. Finally, outcomes

of resting-state functional connectivity pre-and post-treatment will be extracted to observe treatment effect.

Figure 1

PRISMA 2009 Flow Diagram: Literature Search Process



Note: The literature search process is illustrated in a PRISMA 2009 Flow Diagram. Adapted from Moher et al. (2009).

Results

Five articles met the inclusion criteria for this systematic review, and were therefore included for further investigation (Cui et al., 2021; Fu et al., 2015; Li et al., 2013; 2020; Wang et al., 2014). All studies did use a "longitudinal case-control study" design, and investigated in the antidepressant effect on DMN connectivity in MDD patients' pre-and post-treatment. All studies observed connectivity alterations at baseline in MDD patients with respect to healthy control subjects. Antidepressant treatment was successful with connectivity results significantly similar to healthy controls, and reduced depressive symptoms in accordance with HAMD-17. This and further clinical information has been summarized in Table 1. DMN connectivity pre-and post-treatment has been summarized in Table 2.

Clinical Results

All patients had a total score of 17 or above in HAMD-17 at baseline. All studies administered either SSRIs or SNRIs antidepressants' for each participant that were free of antidepressants' at baseline. All studies used healthy control subjects with matched sex, age and educational level (Cui et al., 2021; Fu et al., 2015; Li et al., 2013; 2021; Wang et al., 2014). Control subjects had no history of neurological or psychiatric disorders, with total score of ≤ 7 on HAMD-17 at baseline and post-treatment, hence did not meet any MDD criteria (Cui et al., 2021; Fu et al., 2015; Li et al., 2013; 2020; Wang et al., 2014).

Two studies administrated SSRI citalopram as antidepressant treatment; one with a dose range of 10-30 mg/day during eight weeks (Wang et al., 2014), and one with 5-20 mg/day during 12 weeks (Cui et al., 2021). One study administered SNRI duloxetine as their antidepressant treatment, with 60-120 mg/day during a 12 week period (Fu et al., 2015). Two studies investigated both SSRI and SNRI antidepressants' (Li et al., 2013; 2021). One with a 12 week treatment period administrating either 20-60 mg/day SSRI paroxetine, 75-225 mg/day SSRI venlafaxine, or 60-90 mg/day SNRI duloxetine (Li et al., 2013). The other study progressed during eight weeks, with either SSRI citalopram 10-17.3 mg/day (n = 23), or SNRI duloxetine 52.9-62.9 mg/day (n = 36) as antidepressant treatments (Li et al., 2021).

Table 1

Clinical Information and HAMD-17 score

Study (author, year)	**Clinical sample** (diagnosis, sample size (m/f), mean age and SD)	**Treatment** (period, treatment)	**Control sample** (sample size (m/f), mean age and SD)	**Pre HAMD-17** (mean score and SD)	**Post HAMD-17** (mean score and SD)
Li et al. (2013)	MDD *n* = 24 (8/16) 31.83 ± 11.11	12 weeks SSRI: Paroxetine (20-60mg) Citalopram (20-40mg) SNRI: Venlafaxine (75-225mg) Duloxetine (60-90mg)	*n* = 20 (9/20) 33.62 ± 10.29	26.42 ± 5.22	5.13 ± 1.26
Li et al. (2021)	MDD *n* = 40 (19/21) 30.23 ± 8.21	8 weeks SSRI: Citalopram (10-17.3mg) SNRI: Duloxetine (52.9-62.9mg)	*n* = 85 (31/54) 29.54 ± 9.04	24.43 ± 4.19	4.88 ± 3.58
Wang et al. (2015)	MDD *n* = 20 (9/11) 34.6 ± 12.2	8 weeks SSRI: Citalopram (10-30mg)	*n* = 20 (9/11) 33.3 ± 10.3	20.0 ± 0.9	5.8 ± 1.6
Cui et al. (2021)	MDD *n* = 36 (11/25) 27.5 ± 5.88	12 weeks SSRI: Citalopram (5-20mg)	*n* = 64 (22/39) 26.16 ± 4.38	21.86 ± 3.25	8.11 ± 5.04
Fu et al. (2014)	MDD *n* = 21 40.2 ± 11.2	12 weeks SNRI: Duloxetine (60-120mg)	*n* = 20 38.8 ± 9.9	22.4 ± 2.7	8.5 ± 7.0

Note. (m/f), male/female; n, sample size; SD, standard deviation; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; HAMD-17, Hamilton Depression Rating Scale

DMN Hyper Connectivity Pre-Treatment

DMN hyper connectivity were found at baseline in MDD patients with respect to healthy controls in three studies (Li et al., 2013; 2020; Wang et al., 2015). In the study by Li et al. (2013) pre-treatment connectivity results suggest hyper connectivity in medial PFC in the anterior region, and bilateral precuneus located in the posterior region. Li et al. (2021) observed pre-treatment results of hyper connectivity within all their regions of interest, namely inferior parietal lobule located in ventral DMN, posterior cingulate cortex in posterior DMN, ventral and medial prefrontal cortex located in the core, and lateral temporal cortex in the anterior regions of the DMN. Wang et al. (2014) suggest hyper connectivity mainly anteriorly involving dorsal medial PFC, posteriorly in posterior cingulate cortex, and ventrally in the inferior parietal lobule. Moreover, significant group effect on functional connectivity were observed in the right medial frontal gyrus, right supplemental motor area and right parahippocampal gyrus.

DMN Hypo Connectivity Pre-Treatment

DMN hypo connectivity was found in three studies pre-treatment (Cui et al., 2021; Fu et al., 2015; Wang et al., 2014). Hypo as well as hyper connectivity were found pre-treatment in the study conducted by Wang et al. (2014). Connectivity in bilateral hippocampi were significantly lower in MDD patients with respect to healthy controls. MDD patients also had lower activity between anterior and ventral regions; in left superior temporal gyrus, right angular gyrus, and occipital regions. Moreover, dorsal medial PFC located in the core subsystem was found hyper active in MDD patients with respect to healthy controls. On the contrary, Cui et al. (2021) observed reduced connectivity in dorsal medial PFC. In the paper by Fu et al. (2015), hypo connectivity were observed in ventral regions of the DMN, mainly in bilateral subgenual anterior cingulate, also in parahippocampal gyrus, angular gyrus, right hippocampus and middle occipital gyrus, and frontal pole in the anterior regions of the network.

Increased DMN Connectivity Post-Treatment

Increased DMN connectivity was found post-treatment in MDD patients with respect to healthy controls (Cui et al., 2021; Fu et al., 2015; Wang et al., 2014). Connectivity patterns were suggested to be spatially significantly similar across both groups (Cui et al., 2021; Wang et al., 2014). In the study conducted by Wang et al. (2014), altered connectivity increased in hippocampi bilaterally located in the ventral subsystem. Cui et al. (2021) observed increased connectivity in dorsal medial PFC, located in the core subsystem, following treatment. Fu et al. (2015) found increased connectivity in and between DMN components in medial prefrontal regions, located in the anterior sub region; namely subgenual cingulate, pregenual,

and the frontal pole, and right hippocampus, parahippocampal gyrus, angular gyrus, and middle occipital gyrus.

Reduced DMN Connectivity Post-Treatment

In three out of five studies, reduced DMN connectivity were observed post-treatment in MDD patients (Li et al., 2013; 2020; Wang et al., 2015), significantly similar to the health control subjects. Li et al. (2013) observed reduced connectivity in bilateral precunues, located in the posterior subnetwork of the DMN. In the latter study by Li et al. (2021), reduced connectivity were observed in medial PFC in the anterior part of the DMN, posterior cingulate cortex in the posterior sub region, and inferior parietal lobule in the ventral sub network of the DMN. In the study conducted by Wang et al. (2015) reduced connectivity were observed bilaterally in dorsal medial PFC, located in anterior DMN.

Table 2

Connectivity Results Pre-and Post-Treatment

Study (author, year)	**fMRI design**	**FC pre-treatment** (in MDD patients)	**FC post-treatment** (in MDD patients)
Li et al. (2013)	Rest with eyes closed	Hyper connectivity: precuneus, mPFC	Reduced connectivity: Precuneus
Li et al. (2021)	Rest with eyes closed	Hyper connectivity: IPL, PCC, mPFC, LTC	Reduced connectivity: mPFC, PCC, IPL
Wang et al. (2014)	Rest with eyes closed	Hypo connectivity: bilateral hippocampi Hyper connectivity: dmPFC	Increased connectivity: bilateral hippocampi Reduced connectivity: dmPFC
Cui et al. (2021)	Rest with eyes closed	Hypo connectivity: dmPFC	Increased connectivity: dmPFC
Fu et al. (2105)	Rest with eyes closed	Hypo connectivity: sACC	Increased connectivity: mPFC regions

Note. mPFC, medial prefrontal cortex; IPL, inferior parietal lobule; PCC, posterior cingulate cortex; LTC, lateral temporal cortex; dmPFC, dorsomedial prefrontal cortex; sACC, subgenual anterior cingulate; FC, functional connectivity; MDD, major depressive disorder.

Clinical Improvement and Connectivity Changes

The significantly reduced symptomatic scores according to HAMD-17 following treatment seen in the study by Li et al. (2013) were positively correlated with changes in connectivity seen in MDD patients. In the other study by Li et al. (2021), MDD patients showed substantial reduction in HAMD-17 score of ≤7. The degree of improvement in clinical symptoms from baseline to post-treatment were suggested to have a positive correlation with connectivity change following treatment. In the same study, patients who responded better showed less decrease in connectivity following treatment. Wang et al. (2014) suggested results of significantly reduced connectivity following treatment positively correlated with the symptomatic improvement. In the study by Fu et al. (2015) observations of significant symptomatic improvement correlated negatively with changes in connectivity following treatment. Further, results indicated on patients with reduced connectivity in subgenual anterior cingulate at baseline showed the greatest clinical improvement following treatment. Cui et al. (2021) observed significantly reduced scores following treatment indicating on a significant negative correlation with resting state connectivity. Additionally, low resting state connectivity was associated with good clinical improvement.

Discussion

The aim of this systematic review was to compile findings on resting-state DMN connectivity in MDD patients' pre-and post-treatment. The main question was to clarify effects of SSRI and SNRI antidepressants' on DMN connectivity pre-and post-treatment, and find a possible association between connectivity changes and symptomatic improvement. Findings and limitation will further be contextualized and discussed in relation to current state of research evidence, also in relation to societal and ethical aspects.

Implication of Results

A wide range of altered DMN connectivity was found at baseline in this current systematic review. Connectivity patterns at baseline suggested hypo connectivity (Cui et al., 2021; Fu et al., 2015), hyper connectivity (Li et al., 2013; 2021), and both connectivity patterns coexisting (Wang et al., 2014) in all of the sub regions of the DMN. Post-treatment results on resting-state DMN connectivity, and total scores of HAMD-17 was observed as significantly similar to healthy controls. These results allow us to conclude that a correlation was found between symptomatic improvement and changes in DMN connectivity (Li et al., 2013; 2021; Cui et al., 2021; Fu et al., 2015; Wang et al., 2014). Results are in alignment with previous research.

Hyper Connectivity Pre-Treatment

This systematic review investigated two studies conducted by Li et al. (2013; 2021). There were several aspects found similar between the two studies. Both included both SSRIs and SNRIs as antidepressant treatment, and baseline results from both studies suggested hyper connectivity in anterior and posterior sub regions. Abnormally high connectivity observed pre-treatment was found to decrease following antidepressant treatment. Additionally, no significant difference were found between the two groups, administrated to either SSRIs or SNRIs.

However, one relevant difference between the two studies was the normalization effect on connectivity following antidepressant treatment. In the first study, antidepressant treatment seemed to normalize anterior regions of the DMN, however, posterior regions tended to stay altered. In the latter study, hyper active connectivity in both anterior and posterior regions decreased, and was observed as significantly similar to healthy controls.

These results allow us to conclude that antidepressant treatment did not affect all components exhibiting altered hyper active connectivity at baseline. Results are in alignment with previous research, suggesting the so called "normalization hypothesis" as not yet

significantly proven and needs more investigation (Bluhm et al., 2009; Grimm et al., 2009; Sheline et al., 2001; Posner et al., 2013).

Hypo Connectivity Pre-Treatment

Fu et al. (2015) found alterations of hypo connectivity at baseline in the core subsystem, particularly in subgenual anterior cingulate. These results are in alignment with previous research (Kaiser, Andrews-Hanna, Wager & Pizzagalli, 2015). Altered connectivity seemed to reverse following treatment, observed as significantly similar with respect to healthy controls. Moreover, subgenual cingulate cortex was the component most negatively correlated with symptomatic improvements. These results are in alignment with previous research, suggesting subgenual cingulate cortex as a predictor of depression severity, and symptomatic improvement in medication-free MDD patients (Greicius et al., 2007; Bluhm et al., 2009; Grimm et al., 2009). Further thoughts are brought up regarding hypo connectivity seen in MDD patients. Henceforth, the DMN is known for its ongoing activity associated with mind wandering. As hypo connectivity have been found in MDD patients suffering from severe symptoms as excessive mind wandering, or rumination, it allow us to reconsider the association between mind wandering and increased DMN connectivity. The ongoing activity in the DMN needs further investigation in order deepen our understanding of the networks underlying mechanisms.

Hyper-and Hypo Connectivity Pre-Treatment

Wang et al. (2014) was the only study that found significant connectivity patterns of both hypo-and hyper connectivity before the start of treatment. The most hyper active component found was dorsal medical PFC, followed by decreased activity post treatment observed as significantly similar to healthy control subjects. Wang et al. (2014) also found abnormally low connectivity in bilateral hippocampi, observed to increase following antidepressant treatment. The antidepressant treatment was implicated as a normalization effect on the abnormally high and low connectivity observed pre-treatment. According to Wang et al. (2014), dorsal medial PFC function as an objective indicator of clinical response to SSRI treatment. These results are in alignment with previous research, suggesting dorsal medial PFC to function as a target region for patients diagnosed with MDD.

In the study conducted by Cui et al. (2021), dorsal medial PFC was found to exhibit significantly decreased connectivity patterns, hence also suggesting this component as an objective indicator of clinical response to antidepressant treatment. The two studies suggest either hypo-or hyper connectivity in the same component at baseline. One aspect to consider that might have affected this contradiction is that even though all participants were drug-free at baseline, all studies had their own preference regarding drug-free days before the baseline

scan. As a conclusion, even though patients are drug-free, days or even weeks, before the start of treatment, previous medication might affect brain connectivity at baseline scan, and might be considered to affect connectivity results.

Limitations

This current systematic review has some limitations that may be considered. First, findings might have been affected as the search process depended on the authors' knowledge, hence was not influenced by a second opinion. Variables that might have limited the amount and selection of studies are selection of search string, Boolean operators, and, inclusion and exclusion criteria's. Reconsidering exclusion criteria into inclusion criteria regarding single-dose treatment, and adolescents as participants might have further the number of studies and provided a more diverse, less biased result. Second, administration of personalized dosage of antidepressant treatment at an early stage of treatment period might have affected connectivity results, and also correlations between symptomatic improvement and connectivity changes. Third, two of the studies (Li et al., 2013; 2021) administrated both SSRI and SNRI antidepressants'. SSRI inhibits serotonin reuptake, and SNRI inhibits both serotonin and norepinephrine reuptake, although no difference were found between the two groups, decreased connectivity observed in both studies do now partly supports a more critical role for the serotonin reuptake inhibition. Lastly, inconsistent connectivity patterns at baseline might have been affected by different interpretations of drug-free days before the start of treatment, hence been affecting connectivity patterns.

Societal and Ethical Aspects

MDD patients belong to a socially vulnerable population, in a large extent affected by social and ethical aspects. To minimize the risk of harm and consequences following MDD patients' participation in research experiments, raising societal and ethical issues should be considered important. Issues to bring up regards patients' safety and autonomy. Mental health disorders may affect patients' ability to resonate in societal and ethical aspects (Andrews-Hanna et al., 2010; Cheng et al., 2016; Fu et al., 2015). Therefore, these symptoms may result in difficulties like decision making for themselves, and by only involving experienced psychiatrists might reduce aspects of therapeutic misconception. MDD patients' dependence on clinicians to attend to their best interest in ethics and law is of high importance for confidentiality. Moreover, medical side effects of antidepressants' might negatively affect patients' mental health. Administration of appropriate antidepressant treatment might reduce side effects of increased risk of serious behavioural outcomes, such as suicide. This issue concerns all patients suffering from MDD, although, young individuals are more exposed to this issue.

Future Research

There are some considerations needed for future research that may evaluate and further the understanding of the DMN in disease. Placebo controlled trials to investigate antidepressant treatment should be considered as the antidepressant effect may be implicated as more significantly quantified. Moreover, SSRIs and SNRIs are widely considered antidepressants' in the pharmaceutical industry, however, recent promising antidepressants', such as ketamine (known as N-methyl D-aspartate; NDMA receptor blockers) should be investigated as future first-line antidepressants. Even though the pharmaceutical industry and trials imply extreme costs, investigating in antidepressants' may improve common and sever psychiatric disorders. As results from this study indicates on no significant difference between SSRIs and SNRIs, first-line antidepressants' needs further investigation in order to improve personalized treatment. Results from this systematic review shows promising results that are in alignment with previous research, however, follow ups should be considered as important, as connectivity changes, hence symptomatic improvement are not permanent.

Conclusion

The aim of this systematic review was to investigate resting-state connectivity within the DMN in MDD patient's pre-and post-antidepressant treatment. Baseline results suggested both hypo-and hyper active connectivity, while altered connectivity seemed to normalize following treatment with one exception in medial prefrontal regions. Connectivity changes correlated with symptomatic improvements. Results are in alignment with previous research suggesting DMN as an important network in understanding MDD. For more significantly quantified results regarding DMN connectivity pre-and post-treatment, future research should consider placebo controlled trials.

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