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# **Together alone:**

## **Social dysfunction in neuropsychiatric disorders**

**Ilja Maria Josephien Saris**

VRIJE UNIVERSITEIT

## Colofon

This thesis was prepared at the Department of Research and Innovation at GGZ inGeest, and the Department of Psychiatry, Amsterdam UMC, location VUmc, Amsterdam, within the Amsterdam Public Health research institute.

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## TOGETHER ALONE: Social dysfunction in neuropsychiatric disorders

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## Chapter 1

# Introduction

**Case 1:** A 45-year-old, married man and father presents himself on the psychiatric outpatient clinic. His mood is depressed most of the day and feels sad since he lost his job 5 months ago. He is experiencing sleep problems, loss of energy and loss of weight. He is avoiding contact with friends and family. He finds it hard to initiate activities with his wife and children and spends most of his time walking alone or sitting on the couch.

.....

**Case 2:** A 24-year-old male student is increasingly involved in an invisible society. He hears voices in his head and receives secret messages from this society. Since he started to receive messages, his level of functioning in work and self-care has been reduced. Over the last couple of months, he has been withdrawing himself more and more from social contacts, even before the voices. He feels lonely, stays inside most of the time and has few social interactions.

.....

**Case 3:** A 64-year-old, married woman and (grand)mother experiences more and more problems at work. She does not seem to understand digital changes, is irritable and is proclaimed burned-out. After work, she spends most of her time at home and experiences memory problems; things appear to move around the house and she struggles with using common household equipment. In the last months she is increasingly isolating herself, without initiative to maintain friendships or social contacts.

Major Depressive Disorder (MDD), Schizophrenia (SZ) and Alzheimer's disease (AD) are just three neuropsychiatric disorders that cause an overwhelming public health challenge. As described in the first Global Burden of Disease study in 1990, neuropsychiatric disorders including dementia, neurological disorders, mental and substance use disorders accounted worldwide for more than a quarter of all non-fatal burden, described in years lived with disability.<sup>(1)</sup> The most recent Global Burden of Disease data show that MDD patients have the most years lived with disability.<sup>(2,3)</sup> SZ holds first place for most years of life lost.<sup>(2)</sup> AD is the primary cause of dementia with an estimated 40 million people suffering dementia worldwide, a number expected to double every 20 years until at least 2050.<sup>(4)</sup> Together, MDD, SZ and AD have a major impact on society with ever increasing economic loss, decreased quality of life, not to mention the burden placed on the lives of family members and friends. There is a pressing need for increased understanding of underlying etiology and the creation of more effective treatments. Although the underlying pathophysiology differs among these mental illnesses, they share important symptomatology, one of which is social dysfunction. This thesis looks at social dysfunction as a possible trans-diagnostic measure for mental illness.

### Social dysfunction in various neuropsychiatric disorders

Healthy social functioning is critical for human survival.<sup>(5)</sup> Severe health consequences ranging from cardiovascular diseases to increased mortality rates are associated with social dysfunction, thus further illustrating its importance.<sup>(6–8)</sup> A meta-analysis using data from over 300.000 individuals, showed that individuals with adequate social relationships have a 50% greater likelihood of survival compared to those with poor quality or insufficient social relationships. Indeed, social dysfunction had a higher correlation with premature mortality than did that of smoking, alcohol consumptions, BMI or drug treatment for hypertension.<sup>(6)</sup>

Social functioning is typically affected in the most prevalent neuropsychiatric disorders, such as major depressive disorder, schizophrenia and Alzheimer's disease.<sup>(9)</sup>

### Major Depressive Disorder (MDD)

MDD is diagnosed according to the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria by a trained healthcare professional. At least one of the symptoms during a discrete depressive episode lasting a minimum of 2 weeks should be depressed mood or loss of interest or pleasure accompanied with five or more other symptoms such as 'markedly diminished interest or pleasure in all or almost all, activities most of the day, nearly every day'.<sup>(10)</sup> Although genetic

and environmental contribution as well as neurotransmitter changes and hypothalamic-pituitary-adrenal (HPA) axis dysregulation have found world-wide, (11) the underlying etiology of MDD remains largely unknown. Social dysfunction in MDD is placed under the umbrella of anhedonia, defined as loss of pleasure.(11,12) Findings in social dysfunction include a reduced desire to communicate, increased sensitivity to peer rejection, problems with emotion decoding and mentalizing.(13,14) Social dysfunction is a persistent symptom of depression, and relieving core symptoms does not necessarily improve social functioning.(15)

### Schizophrenia (SZ)

The DSM-5 current guidelines and criteria to establish a diagnosis of the syndromic concept SZ state that the patient must present with at least one of the following symptoms: “*delusions, hallucinations and/or disorganized speech*” sometimes complemented with “*grossly disorganized or catatonic behavior*”.(10) Schizophrenia is described by incorporating both positive and negative symptoms.(16) The positive symptoms are so-called “gained” symptoms such as hallucinations, delusions; negative symptoms are the “lost” behaviors, such as social withdrawal, blunted affect and speech poverty. The underlying neurobiology in SZ had long been attributed to dysfunction in dopaminergic neurotransmission, as well as the intertwined genetic contributions.(16) Recently, this theory has become more nuanced by adding the importance of environmental circumstances and other dysregulations in the brain.(16,17) Pharmacological treatment tends to improve mostly the positive symptoms. Impairments in social functioning are commonly considered negative symptoms and can occur years before the first psychotic episode and tend to be chronic.(16,18) The social impairments described in SZ include problems with mentalizing, social withdrawal, regulating emotions and emotion decoding.(19,20)

### Alzheimer’s disease (AD)

According to the NIA-AA guidelines, an AD diagnosed is established using neuropsychological testing and assessment of symptoms over time to identify the extent of memory loss which ultimately characterizes end stage AD.(21) AD pathology is typically described by reduced hippocampal volume and presence of biomarkers such as cerebrospinal fluid levels of lower amyloid  $\beta_{42}$ , higher total tau and higher phosphorylated-tau. Although it is evident that the amyloid  $\beta$  and tau are the main component of plaques and tangles, little is known about the cause of Alzheimer’s disease. Environmental factors have increasingly been recognized as risk factors in addition to the well-established *APOE<sub>4</sub>* genetic

risk factor amongst other genetic risk factors.(4) In addition to the dementia, up to 80% of the AD patients experience neuropsychiatric symptoms such as apathy, aggression or social withdrawal.(22) Social dysfunction in AD patients is commonly grouped with the neuropsychiatric symptoms.(23) Social dysfunction in an early disease phase is usually more subtle in AD patients, but increases over time as the disorder progresses.(24,25) Social dysfunction tends to start with refined impairments in emotion decoding and mentalizing.(25) Interestingly, AD patients have a more positive perception of their own social functioning than their caregivers do. Furthermore, the social impairments are most burdensome for caregivers.(24,26)

Social dysfunction is present in all three neuropsychiatric disorders, although these disorders differ in other core symptoms and known underlying neurobiology. Interestingly, social dysfunction is also present in other neuropsychiatric disorders, such as (social) anxiety disorder, Parkinson’s disease and multiple sclerosis.(27–29) However, within each disorder social dysfunction is typically categorized fitting in a disease specific cluster of symptoms. Social dysfunction in MDD is frequently grouped as ‘anhedonia’, in SZ as ‘negative symptoms’ and in AD it is grouped under ‘neuropsychiatric symptoms’ or even feelings of guilt and shame about the increasing memory impairments. Sadly, the clusters of symptoms that include social dysfunction are often associated with poorest outcomes, such as functional impairment, disease progression, caregiver burden and quality of life.(23) Furthermore, social dysfunction negatively impacts the lives of patients and their caregivers, as well as the disease trajectories, and is of paramount importance for recovery according to patients.(19,24,26,30–32)

In sum, similarities in social dysfunction seem apparent across major neuropsychiatric disorders. In this thesis, we ask ourselves: Is social dysfunction a disorder-specific phenomenon, or could this be a transdiagnostic symptom?

### Social dysfunction as a trans-diagnostic symptom

What is a transdiagnostic symptom? A transdiagnostic symptom is a symptom that is present across disorders. However, a clear understanding of what transdiagnostic research exactly entails, is still under debate and clear guidelines are lacking.(33,34) One of the proposed, stringent guidelines for transdiagnostic research are the four Mansell criteria: (1) It describes both a clinical, and (2) a non-clinical sample, (3) it must be present in at least four disorders and (4) the transdiagnostic construct must be demonstrated in all mental disorders investigated.(35) The primary aim is to understand shared and overarching processes present across disease (Figure 1) categories.

Since social dysfunction as examined in this thesis fulfills all four Mansell criteria the term trans-diagnostic will be used. Fever can be used as an interesting example of a trans-diagnostic phenotype. A fever can occur for many different reasons. It can be because of local problems such as erysipelas, a systemic problem such as the flu, cancer such as leukemia or immunological problems such as rheumatoid arthritis. However, this common – trans-diagnostic - symptom has a large impact on the outcome of the different disorders. Perhaps more importantly, this specific trans-diagnostic phenotype can be treated independently from the origin of the disorder itself, although that would not solve the disorder. This is how social dysfunction can be conceptualized as well, a possible trans-diagnostic phenotype that impacts the outcome of different disorders, and hopefully in the future can be treated independent from the disorder in question.

The study into trans-diagnostic symptomatologies in psychiatry has taken a leap forward with the introduction of the Research Domain Criteria (RDoC) and the EU ROAMER initiative.(36,37) Since the 1980's the DSM nosological categories based on clinical consensus has increasingly shaped the scientific approaches in psychiatric research.(38) As currently used and described in the DSM-5, nosological categories have provided a way of communicating among professionals around the world, both in the clinical field and in research, progressing psychiatric standards. However, these nosological categories are unable to pinpoint specific underlying neurobiology for psychiatric disorders, thereby precluding the development of novel treatments and precision management.(39,40) A trans-diagnostic approach, originally adapted to foster relevant science, promises a more personal and dimensional approach to (mal)adaptive behavior.(38) Therefore, the RDoC approach was proposed, focusing on six constructs within the field of psychiatry, one of which being the so-called social processes domain.

Social Dysfunction as a possible trans-diagnostic phenotype in MDD, SZ and AD

The first part of this thesis focusses on social dysfunction as a possible trans-diagnostic phenotype in MDD, SZ, and AD. Despite psychopathological differences in manifestation or severity of disease symptoms, there may be an underlying substrate with alike symptoms across disorders.

To examine social dysfunction as a trans-diagnostic phenotype, first we must establish in what way social processes may be similar or different in various neuropsychiatric disorders. Previous studies investigating social dysfunction have been primarily disorder-specific and little consensus exists on how to capture

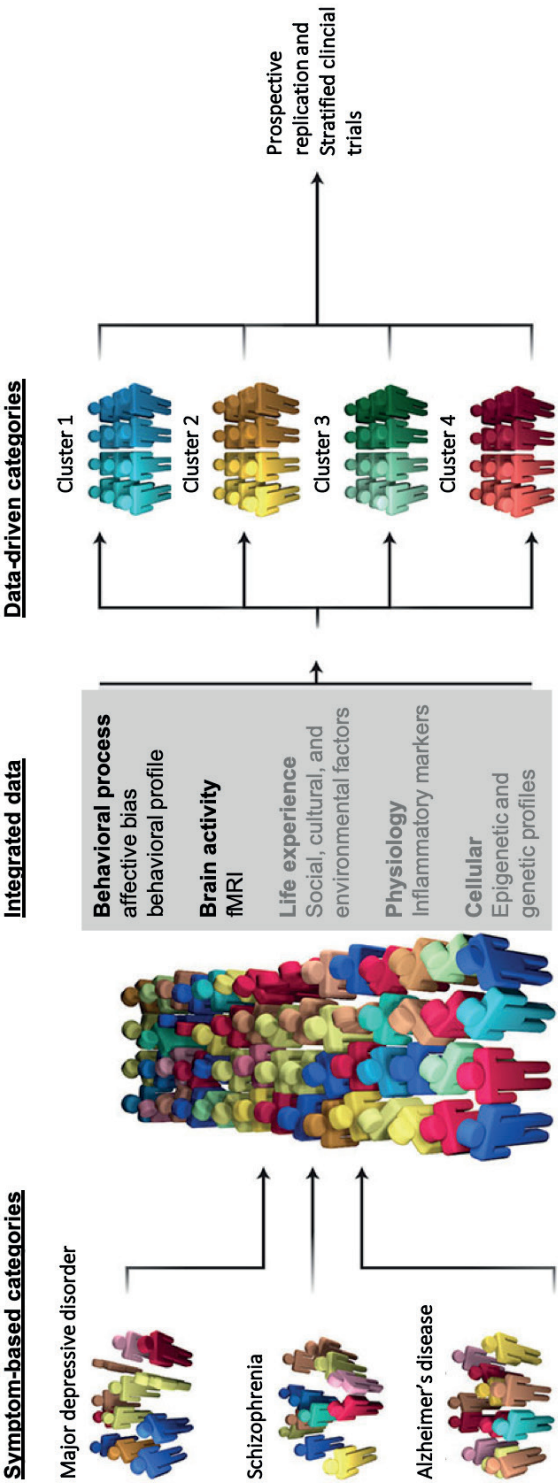


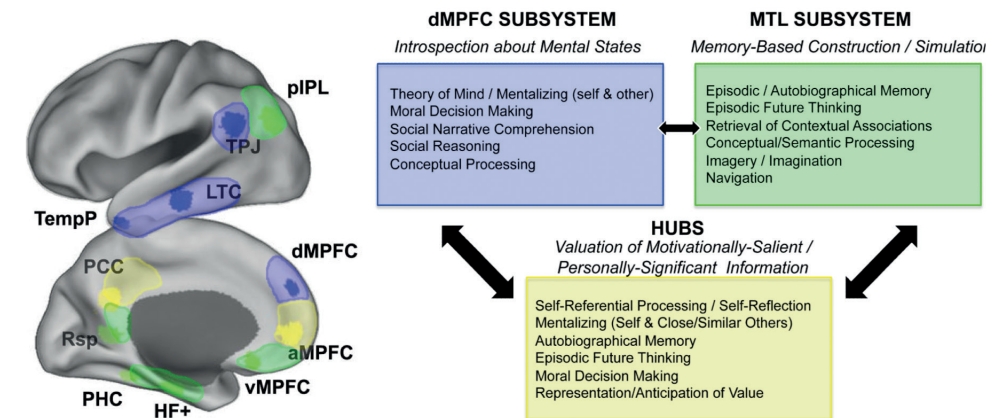
Figure 1: Precision medicine in neuropsychiatry. Hypothetical example illustrates how precision medicine can deconstruct nosological categories into data-driven categories using integrated data, with its main output being prospective replication and stratified clinical trials. This could advance our understanding of neuropsychiatric disorders, thereby aiding clinical care and development of novel (pharmacological) treatments. (Adapted from Insel & Cuthbert 2015, Science)

this notoriously complex construct trans-diagnostically. The neurobiological underpinning for a subjective evaluation of social interactions is thought to differ from a more quantitative behavioral social interaction. Therefore, in an attempt to integrate neurobiological hypotheses and clinical presentations, we opted for selecting certain behavioral and affective markers of social dysfunction.(7,14,41) Behavioral aspects of social dysfunction are quantitative and more objective, for example: social network (number of friends), frequency of social and recreational activities. Affective aspects of social dysfunction on the other hand are thought to be more qualitative and subjective, for example: feelings of loneliness, affiliation and perceived social disability. The affective aspects of social dysfunction are a stronger predictor for poor health and quicker disease progression, while the behavioral aspects seem more predictive of brain dysfunctions.(23,42–44)

### Neurobiological correlates of social dysfunction

But, how can we understand trans-diagnostic social dysfunction? What is happening inside the brain? Is there a neuro-bio-behavioral system underlying this social dysfunction? One of the primary suspects of a neurobiological substrate underlying social dysfunction in MDD/SZ/AD is the brain's default mode network (DMN).

Even when we are not focused on the external environment and let our minds wander, the brain is continually active. (45–48) It is during those moments of mind wandering that our brain is actively working. Indeed, we use 20% of total blood flow just for our brain when we are at rest.(49) The DMN is one of the core intrinsic functional brain networks that is activated, such as during those moments of mind wandering. Marking the beginning of the DMN research, Raichle and colleagues performed MRI scans on participants and observed increased regional blood flow and oxygen consumption, indicating increased metabolic activity in designated brain areas when participants were not performing a task, but rather let their minds wander. Their observation was the opposite of what was expected and commonly believed.(50) They named it "a default mode of brain function".(48) It initiated a new field for neuroscience with ever increasing literature on the DMN. To date, neuroscientists all over the world are still aiming to unravel the function of the DMN. Following common practice in the field, the function of the DMN is largely derived from the anatomical brain areas involved.(50,51)



**Figure 2: DMN neurobiological system.** Left panel: a schematic indication of the DMN with the core hubs (in yellow) with the anterior medial prefrontal cortex (aMPFC), posterior cingulate cortex (PCC). The medial temporal (MTL subsystem) in green include the retrosplenial cortex (Rsp), the parahippocampal cortex (PHC), hippocampal formation (HF+), anterior and ventromedial prefrontal cortex (aMPFC and vMPFC respectively) and the posterior inferior parietal lobule (pIPL). The dorsomedial subsystem (dMPFC subsystem) in blue include temporoparietal junction (TPJ), lateral temporal cortex (LTC), temporal pole (TempP) and the dorsal medial prefrontal cortex (dMPFC). Right panel: schematic illustration of the suggested functions of the components and tasks that activated the components. Arrows indicate approximate strength of connectivity between the components. (Adapted from Andrews-Hanna, Smallwood, & Spreng, 2014, Ann NY Acad Sci. With permission.)

The brain's DMN comprises one mediating core and two subsystems; the dorsal medial and medial temporal subsystems (Figure 2). The core constitutes the posterior cingulate cortex, angular gyrus and rostromedial prefrontal cortex (rmPFC), and mainly supports self-referential, personal processes, along with subsystem coupling. It is involved in integrating internally and externally salient stimuli with social context.(45,47) The dorsal medial subsystem (dmPFC system) includes the dorsomedial PFC (dmPFC), temporoparietal junction (TPJ), lateral temporal cortex, temporal poles and inferior frontal gyrus. It is mostly involved in higher-order social processes such as theory of mind (ToM), mentalizing and social reasoning. The medial temporal subsystem (MTL subsystem) includes the hippocampus, parahippocampal cortex, retrosplenial cortex and posterior inferior parietal lobe. It primarily supports recollection of experiences, past and future autobiographical thought and memory. Typically, during moments of mind wandering, people tend to think about life events in the recent past, present or immediate future and reconstruct scenes based on memories.(51) It has been

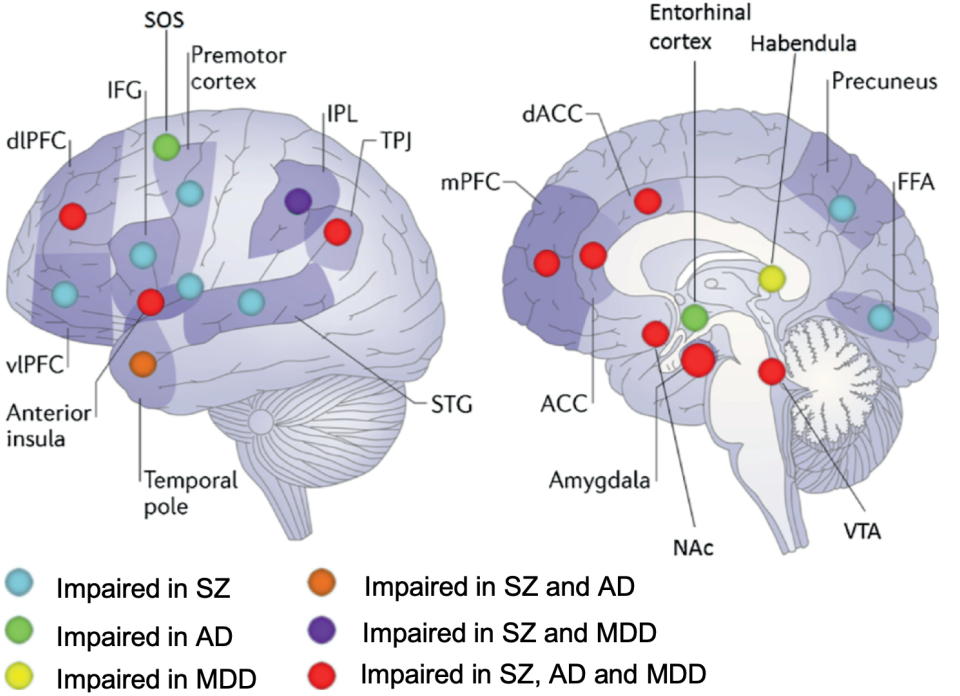
suggested that the highly intertwined DMN subsystems allow for integration of one’s experiences, memories or mental state to form and update models of our (social) experiences to prospectively adapt to new social situations.(47) In short, the DMN is linked to self-referential processes, mentalizing and our ability to navigate the complexities of the social world.(47,52–54) In addition to above mentioned within network findings, white matter tracts and circuits of the “social brain” are also strongly represented in the DMN regions, further echoing the relevance of DMN to human social behavior.(55)

Dysconnectivity patterns of the DMN have been established in various neurological and psychiatric disorders as well as in social dysfunction. As Kaiser and colleagues stated(56) “specific patterns of network dysfunction may contribute to core deficits in cognitive and affective functioning that are believed to underlie clinical symptoms.” This implicates that disturbances in one subsystem or network may cause widespread disruptions in other networks, with an accumulation of similar dysconnectivity patterns, perhaps giving rise to similar clinical symptoms.(56,57) Disruptions in the DMN of MDD, SZ and AD patients is a growing field of study in itself, with the most relevant findings described in several excellent review papers. (9,56,58–63) These findings mainly converge on dysconnectivity patterns along cortical midlines section of the DMN, with a variation of increased and decreased connectivity being reported. However, dysconnectivity patterns are not restricted to the DMN and psychopathology is commonly understood in terms of within- and between-network anomalies.(57,63,64) As claimed in the “Triple Network Model of Psychopathology” most psychiatric disorders such as MDD, SZ and AD are underpinned by within- and between-network interferences involving the DMN, Central Executive network (CEN) and the Frontoparietal Network (FN).(63) Although several networks are involved in psychopathology, none are as strongly associated with social dysfunction and psychopathology as DMN.

Adaptive social functioning is consistently linked with connectional integrity of the DMN, with a profound role for the medial prefrontal cortex.(52–54,65) It has been suggested that higher order social processes such as mentalizing take place ‘higher in the brain’ within the dorsal medial prefrontal cortex as part of the DMN. The more primary social processes such as emotion recognition are thought to occur ‘lower in the brain’ i.e. ventral medial PFC which is part of the medial temporal subsystem of the DMN.(52,53) The subregions of the mPFC as part of the DMN contribute differently to social functioning according to their roles in different subsystems. (52) Interestingly, brain areas (outside the DMN) linked to social dysfunction are often part of the same neural networks affected in MDD, SZ and AD (Figure 3)(9), further strengthening the hypothesis that similar symptoms might give rise to

similar network dysconnectivity patterns.(66) Dysconnectivity patterns for MDD, SZ and AD, as well as for social dysfunction, have been often described; yet a trans-diagnostic approach towards social dysfunction in these disorders remains lacking.

In short, the DMN is seen as one of the key neurobiological systems that might in part be accountable for social dysfunction across major neuropsychiatric disorders. A thorough trans-diagnostic examination of DMN-social dysfunction relationships in MDD, SZ and AD is currently lacking. The second part of this thesis focusses on the possible association of social dysfunction with the DMN in MDD, SZ and AD.



**Figure 3: Brain areas associated with social processes impaired in SZ, AD and MDD as well as their combinations** (Adapted from Porcelli 2019, originally from Green 2015). ACC = anterior cingulate cortex; dACC = dorsal anterior cingulate cortex; dIPFC = dorsolateral prefrontal cortex; FFA = fusiform face areal; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; NAc = nucleus accumbens; TPJ = temporoparietal junction; SOS = superior orbital sulcus; STG = superior temporal gyrus; vIPFC = ventrolateral prefrontal cortex; VTA = ventral tegmental area

CENTRAL AIM AND RESEARCH QUESTIONS OF THIS THESIS

The research gaps described above have led to the formulation of the general aim and research questions of this thesis.

.....  
**General aims:**  
*Is social dysfunction a transdiagnostic trait in neuropsychiatric disorders? And if so, is there a neurobiological substrate associated with this transdiagnostic trait?*  
.....

These general aims translate into two specific research questions:

- 1. What are the commonalities and differences in social dysfunction in major depressive disorder, schizophrenia and Alzheimer’s disease?
- 2. Is the default mode network (DMN) consistently and trans-diagnostically associated with social dysfunction in major depressive disorder, schizophrenia and Alzheimer’s disease?

METHODS

To answer the above mentioned research questions in this thesis, data from two studies are used. Experimental designs, methods and social dysfunction indicators are explained below.

**The Netherlands Study of Depression and Anxiety (NESDA)**  
NESDA is a longitudinal naturalistic multisite cohort study, set up to provide more insight into the long-term course and consequences of depression and anxiety disorders.(67) Recruited between 2004 and 2007, a total of 2981 participants (aged 18-65 years) were enrolled from the Dutch general population (19%), primary health care (54%) and specialized mental health care (27%). Trained researchers conducted the Composite International Diagnostic Interview (CIDI, version 2.1) to confirm the DSM-IV diagnoses of depressive disorders (major depressive disorder or dysthymia) and anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and/or agoraphobia). The included individuals (N=2981) can be divided into five groups: participants without lifetime psychiatric disorders (‘control subjects’, N=652), participants remitted depressive and/or anxiety disorders (‘remitted’, N=628), patients with current (within last month pure anxiety disorders (‘pure anxiety’, N=543) or current pure depressive disorder (‘pure depression’, N=396) or current comorbid anxiety and depressive disorders (‘comorbid’, N=762). Not speaking Dutch language and the presence of clinically overt primary psychiatric disorders (e.g. obsessive–compulsive, psychotic, bipolar, or severe addictive disorders) that might interfere with NESDA’s main aim to examine etiology and course of common depressive and anxiety disorders were exclusion criteria.

Follow-up assessments were performed two, four six and nine years after the baseline measurement. In NESDA, the social questionnaires available were the social activities (5 questions taken from the LASA study), social support, social network size (part of the social support questionnaire), WHODAS ‘getting along domain’, de Jong-Gierveld, loneliness questionnaire, and affiliation questionnaire.(68–72)

The neuroimaging study within NESDA includes baseline data with 120 MDD patients of which 74 participants were available for resting-state analyses. Participants were asked to lie still in the scanner, with eyes closed and not to fall asleep. Wakefulness was confirmed after scanning.



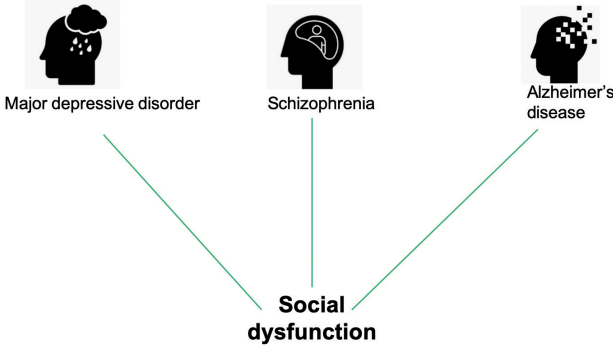
Figure 4: graphic illustration of the PRISM I-project, main aim is to discover separate social withdrawal clusters in SZ and AD patients.

### The Psychiatric Ratings using Intermediate Stratified markers (PRISM)

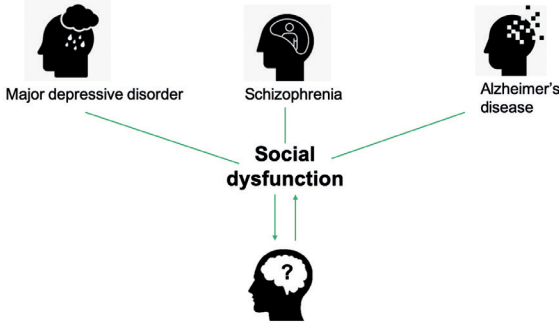
The PRISM study is an European multisite, EU-funded, cross-sectional, transdiagnostic-disorder study to explore possible biomarkers associated of social withdrawal within a schizophrenia and Alzheimer’s disease group as well as two age-matched healthy control groups.(39,73) PRISM was set up to deep-phenotype the participants with behavioral assessments, physiological monitoring, electrophysiology, genetics, brain imaging and smart phone monitoring aimed to unravel social withdrawal into several subtypes of social withdrawal (see also figure 4). In total 163 participants were included of which 56 schizophrenia and 50 Alzheimer’s disease patients. Social questionnaires available from the PRISM study are the Social Functioning Scale, de Jong-Gierveld Loneliness questionnaire, adjusted WHODAS ‘getting along domain’.(41,69,70,74) Resting state scans from PRISM includes data from 150 participants (SZ N=48; AD N=47; healthy controls N=55). Participants were asked to lie still in the scanner, eyes open focusing on a landmark. Wakefulness was confirmed after scanning.

## OUTLINE OF THIS THESIS

This thesis is divided into two parts according to the general aim and research questions formulated above:



In **Part I** we focus on the differences and similarities of social dysfunction in different neuropsychiatric disorders (i.e. MDD/SZ/AD) (please see figure 3). In **chapter 2** we explore social affective and social behavioral social functioning in anxiety and depressed patients, their combination, as well as participants remitted from anxiety and/or depression, in addition to participants without lifetime history of these disorders. **Chapter 3** examines social functioning in SZ and AD patients using behavioral and affective indicators of social functioning.



In **Part II** we explore the role of the DMN in social dysfunction in different neuropsychiatric disorders (i.e. MDD/SZ/AD), as is illustrated in figure 4. **Chapter 4** tests if the DMN is associated with social dysfunction within a group of MDD patients. **Chapter 5** examines if the DMN is associated with social dysfunction within a group of SZ and AD patients, along with age-matched healthy controls.

Finally, **Chapter 6** provides a summary of the main findings, discussion and conclusion.

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## Chapter 2

# Social functioning in patients with depressive and anxiety disorders

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ABSTRACT

**BACKGROUND:** Adaptive social functioning is severely impeded in depressive and anxiety disorders, even after remission. However, a comprehensive overview is still lacking.

**METHODS:** Using data from the Netherlands Study of Depression and Anxiety (NESDA), behavioral (network size, social activities, social support) and affective (loneliness, affiliation, perceived social disability) indicators of social functioning were analyzed in patients with anxiety (N=540), depressive (N=393), comorbid anxiety and depressive disorders, ('comorbid', N=748), remitted participants (N=621) and healthy control subjects (N=650).

**RESULTS:** Analyses revealed an increasing trend of social dysfunction among patient groups, with patients with comorbid anxiety and depressive disorders, showing the most severe impairments, followed by depressed and anxious patients ( $p's < 0.001$  for all social functioning indicators). Affective indicators showed the largest effect sizes (Cohen's d range from 0.13-1.76). We also found impairments in social functioning among remitted patients. Furthermore, perceived social disability among patients was predictive of still having a depressive and/or anxiety diagnosis two years later ( $p < 0.01$ ).

**CONCLUSIONS:** Behavioral but especially affective indicators of social functioning are impaired in patients with anxiety or depressive disorders, and most in patients with comorbid disorders. After remission of affective psychopathology residual impairments tend to remain, while social dysfunction in patients seems predictive of future psychopathology.

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3 Significant outcomes:

- 1. Social functioning is affected in patients with anxiety disorders, even more so in those with depressive disorders, and most prominently in patients with comorbid anxiety and depressive disorders.
- 2. Even after complete remission of affective psychopathology residual impairments tend to remain.
- 3. Perceived social disability among patients is predictive of still having a depressive and/or anxiety diagnosis two years later.

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3 Noteworthy limitations

- 1. Most of our analyses were cross-sectional, thereby not allowing causal inferences.
- 2. More detailed aspects of social functioning, such as the exact composition of the social network were not examined in our study.
- 3. Differences between our findings and previous findings might stem from the use of different measures of symptomatology and social functioning. Ideally, one would have used actual behavioral data, instead of retrospective self-reports.

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## INTRODUCTION

Adequate social functioning is imperative for human well-being and survival,<sup>1</sup> as is reflected by the severe health outcomes associated with social dysfunction, ranging from cardiovascular diseases to increased mortality rates.<sup>2-4</sup> The influence of social functioning on premature mortality is believed to be higher than that of smoking, alcohol consumption or obesity.<sup>3</sup> Not only is social functioning essential for human well-being and survival, it is typically one of the main areas severely affected in common psychiatric disorders, such as depression and anxiety.

Social functioning can be studied in various manners and little consensus exists on how to best describe it.<sup>5</sup> In recent reviews a multidimensional definition is proposed that includes both 'behavioral' and 'affective' indicators of social functioning.<sup>5-7</sup> Behavioral indicators represent objective and quantitative measures of social function,<sup>5</sup> including social network size, frequency of social activities, and frequency of perceived social support. Affective indicators, on the other hand, reflect more subjective and evaluative measures of interpersonal and socio-emotional functioning,<sup>8</sup> and include features such as loneliness, affiliation, and perceived social disability,

Overall, findings on social functioning in depression seem to suggest that affective indicators are more persistently affected compared to the behavioral indicators.<sup>6</sup> Santini et al.<sup>6</sup> showed that perceived support (affective indicator) was more important for social functioning in depression than received support (behavioral indicator), and increased levels of perceived support played a protective role in depression onset. In addition, Cacioppo et al.<sup>8</sup> indicated that loneliness increases the risk for depression. Generally, when compared to healthy controls, patients with anxiety disorders have a lower quality of life especially in the areas of social interactions and subjective well-being.<sup>9</sup> With regard to comparing social functioning between different anxiety disorders, findings are not unequivocal. McKnight et al.<sup>10</sup> showed that anxiety disorders such as agoraphobia and generalized anxiety disorder (GAD) have a stronger association with social isolation than social phobia (SP). This is in contrast to findings that GAD, SP and panic disorder (PD) did not differ in the amount of social impairment<sup>11</sup>, or to the finding that PD was most impaired in social functioning in comparison to other anxiety disorders.<sup>12</sup>

In an estimated 50-70% of the patients, anxiety and depression tend to co-occur (i.e., comorbidity),<sup>13,14</sup> most likely as a result of common underlying pathophysiological processes.<sup>15</sup> When these disorders co-occur, the chronicity and functional impairments rise substantially.<sup>16-18</sup> Yet, even though social dysfunction is among

the most pervasive and debilitating symptoms of affective psychopathology and tends to persist long after remission, a thorough examination of social functioning in clinically anxious or depressed patients, as well in those presenting comorbidity and those in remission, is currently lacking.<sup>19-22</sup>

### Aims of the study

Impairments of social functioning are typically examined separately for depressive and anxiety disorders, thereby not providing a comprehensive examination of differences and commonalities in social functioning in these disorders. We addressed this important issue, by comparing social functioning indices across five large groups of participants, including patients with either pure depression or anxiety disorders, as well as their combination (comorbid), along with remitted patients and healthy control participants. First, we examined to what extent various behavioral and affective indicators of social functioning are affected in patients with depression, anxiety or comorbid disorders, as compared to healthy controls. Second, we examined to what extent these aspects of social functioning were still impaired in individuals remitted from these disorders. Third, we examined how clinical characteristics such as type of disorder (depression, panic, social phobia or generalized anxiety disorder), severity, age of onset and duration of disorder, are associated with the level of social functioning. Fourth, we examined whether social dysfunction among patients is predictive of still having a clinical diagnosis of anxiety or depression after two years.

## MATERIALS AND METHODS

### Study sample

Data for the current study were derived from the ongoing Netherlands Study of Depression and Anxiety (NESDA). NESDA is a longitudinal naturalistic cohort study, set up to provide more insight into the long-term course and consequences of depression and anxiety disorders. Recruited between September 2004 and February 2007, a total of 2981 participants were enrolled from community care, primary care and specialized mental health care from three regions in the Netherlands. The study includes individuals without lifetime psychiatric disorders ('control subjects') and participants with current or remitted depressive and anxiety disorders or comorbid anxiety and depressive disorders. Not speaking Dutch language and the presence of clinically overt primary psychiatric disorders (e.g. obsessive compulsive, psychotic, bipolar or severe addictive disorders) that might interfere with NESDA's main aims to examine etiology and course of common depressive and anxiety disorders were exclusion criteria.

The study was approved by the Ethics Review Board of the VU University Medical Centre Amsterdam and by the local review boards of all participating centers. All participants gave their verbal and written Informed Consent. A more detailed description of NESDA is described elsewhere.<sup>23</sup> We excluded 29 participants for whom no information on social functioning was available. Thus, baseline data from 2952 Participants were used for cross-sectional analyses. Clinical follow-up data after two years were available for 1409 of the 1681 (84%) patients with a current disorder at baseline.

## Measurements

### *Depressive and anxiety disorders*

The DSM-IV Composite Interview Diagnostic Instrument (CIDI; WHO version 2.1) was used to diagnose major depressive disorder (MDD) and anxiety disorders (panic disorder (PD), social phobia (SP), generalized anxiety disorder (GAD), agoraphobia (AP)). Based on the CIDI information, all 2952 respondents were categorized into one out of five groups. The first group included healthy participants who have no current and past history of psychiatric disorders ('control subjects', N=650). The second group included participants who have had a depressive or anxiety disorder during lifetime, but did not have this diagnosis in the last six months ('remitted', N=621). The third and fourth group consisted of patients with diagnosis of either anxiety ('pure anxiety', N=540) or depressive ('pure depression', N=393) disorder in the last six months. The final group included participants with a comorbid anxiety and depressive disorder in the last six months ('comorbid anxiety and depression', N=748).

### *Clinical characteristics*

The earliest age of onset of disorders was determined using the CIDI. The Inventory of Depressive Symptoms – Self-Report (IDS)<sup>24</sup> was used to assess severity of depressive symptoms in the past week. The Beck Anxiety Index (BAI),<sup>25</sup> was used to assess severity of anxiety symptomatology. The Fear questionnaire (FQ) measured severity of avoidance behavior.<sup>26</sup> The Life Chart method<sup>27</sup> provided more insight into the duration of symptoms in the past four years, estimated by dividing the duration of symptoms (number of affected months) by total number of follow-up month. Course of disorder was additionally measured by the CIDI at the 2-year follow-up assessment. Current antidepressant use and psychotherapy (defined as having > 1 contact with psychologist, social psychiatric nurse or social worker in last six months) were determined by routine questioning.

### *Behavioral indicators of social functioning*

We assessed network category, social activity status and received social support as behavioral indicators of social functioning. Network category was operationalized as the number of adults with whom the participant has a regular and important contact. The

answer is given on a six-point scale; 1 (0 or 1 individuals in network), 2 (2-5 individuals), 3 (6-10 individuals), 4 (11-15 individuals), 5 (16-20 individuals) and 6 (>20 individuals in network). The social activity status is a self-report regarding the frequency of visiting five different social activities (cultural events, trips to nature, visiting restaurants, social meetings, outdoor sport activities), ranging from almost never (1) to several times per week (6). A sum score was calculated adding up the frequency of conducting these five social activities, ranging from 5 to 30. The Close Persons Questionnaire (CPQ) measured the amount of received social support.<sup>28,29</sup> Participants answered ten questions about their partner and a maximum of two confidants. We calculated sum scores per partner or confidant, which were then re-calculated into one mean social support score. For participants whom reported not to have a first (n=662) or second (N=543) confident, questions were scored as 0.

### *Affective indicators of social functioning*

We assessed loneliness, affiliation and perceived social disability as affective indicators of social functioning. The de Jong Loneliness scale<sup>30</sup> describes feelings of loneliness with 11 questions. Affiliation, in other words the perceived connection with others, was measured using the 6-item self-report 'need for affiliation' scale.<sup>31</sup> Perceived social disability was measured using the 5-item social interaction subscale from the World Health Organization Disability Assessment Schedule (WHO-DAS), which includes questions about difficulties in making new or maintaining friendships.<sup>32</sup>

## Statistical analyses

Demographic and clinical characteristics were described and compared using  $\chi^2$  for dichotomous variables and analysis of variance (ANOVA) for continuous variables. The independent Kruskal-Wallis test was used as non-parametric test when assumptions for parametric testing were not met. Spearman correlations described associations between social functioning indicators. Analyses of covariance (ANCOVA's) adjusted for sex, age, years of education, and partner status (having a partner or not) probed for between-groups differences in behavioral and affective indicators of social functioning. Effect sizes were estimated by calculating Cohen's d, comparing clinical groups to healthy controls. To examine the association of clinical characteristics (type of disease, severity, age of onset, duration) with behavioral and affective indicators of social functioning, multiple linear regression analyses in the subgroup of patients with a current disorder were conducted. Different disorders were coded using dummy variables in the linear regression model, this allowed us to eliminate the shared variance between disorder types.

Finally, within current patients of which we had longitudinal data (N=1409), we conducted logistic regression analyses to examine whether social functioning indices at baseline were predictive of the presence of (still) having an affective disorder at two year follow up corrected for covariates (age, sex, educational level, partner status, and in a next model also severity of depression and anxiety). Statistical analyses were conducted using SPSS (IBM, Version 22), and a two-tailed significance level of  $p<0.05$  was considered statistically significant.

RESULTS

The mean age of the study sample (N=2952) was 41.9 years (SD=13.1) and 66.4% were females (Table 1). Controls had a higher level of education and more often a partner than patients. As expected, groups differed significantly in all psychiatric characteristics, with the comorbid group showing the highest scores on all severity measures. Correlation analyses across all subjects revealed strong interrelations between social functioning indices (see Supplementary table 1). In brief, affective social functioning measures such as loneliness and perceived social disability were highly correlated with each other ( $r=0.55$ ), but correlations with affiliation were slightly lower ( $r=-0.32$  for loneliness;  $r=-0.23$  for perceived disability). Affective social functioning indices were significantly correlated with behavioral indices (network size, social activities and social support) with correlations ranging between  $r=0.13$  (affiliation and network size) and  $r=-0.40$  (loneliness and network size).

As shown in Table 2, between-group differences emerged on all measures of social functioning ( $p's<0.001$ ) adjusted for age, sex, education and partner status (for network size  $F(4, 2938)= 50.978, p<0.001$ ; for loneliness  $F(4, 2611)= 173.252, p<0.001$  for perceived social disability  $F(4, 2133)= 274.099, p<0.001$ ). Effect sizes for the significant effects ranged from small to large (Cohen's  $d$  0.13-1.76). Overall, groups differed significantly ( $p<0.001$ ), with a trend visible for all behavioral and affective indicators, as depicted in Figure 1 with unadjusted means. Controls had the highest levels of social functioning and patients with comorbid disorders were the most impaired. Anxiety patients differed from healthy controls on all social functioning indices, with effect sizes larger for affective indicators. This pattern, but even less favorable, was also seen in depressed patients. Patients with comorbidity showed the most severe impairments on all indicators of social functioning, and differed most significantly from healthy controls. Overall, affective indicators revealed larger effect sizes across disease status than behavioral indicators of social functioning.

Table 1: Baseline characteristics (N=2952)

|                                                        | Control subjects<br>N = 650 | Remitted anxiety<br>or depression<br>N = 621 | Pure Anxiety<br>N=540 | Pure Depression<br>N = 393 | Comorbid anxiety<br>and depression<br>N = 748 | p-value |
|--------------------------------------------------------|-----------------------------|----------------------------------------------|-----------------------|----------------------------|-----------------------------------------------|---------|
| <b>Demographics</b>                                    |                             |                                              |                       |                            |                                               |         |
| Age (years), mean (SD)                                 | 41.2 (14.7)                 | 44.4 (12.9)                                  | 41.8 (12.8)           | 41.0 (12.2)                | 41.3 (12.0)                                   | <0.001  |
| Sex (% female)                                         | 61.5%                       | 70.0%                                        | 67.4%                 | 64.9%                      | 68.0%                                         | <0.05   |
| Education (years), mean (SD)                           | 12.8 (3.2)                  | 12.5 (3.2)                                   | 12.1 (3.2)            | 12.2 (3.2)                 | 11.3 (3.3)                                    | <0.001  |
| Partner status (% with partner)                        | 75.1%                       | 74.4%                                        | 67.4%                 | 65.1%                      | 64.2%                                         | <0.001  |
| <b>Psychiatric characteristics</b>                     |                             |                                              |                       |                            |                                               |         |
| Depression severity, mean IDS score (SD)               | 8.5 (7.5)                   | 14.1 (9.0)                                   | 22.0 (9.7)            | 27.8 (11.3)                | 34.9 (12.2)                                   | <0.001  |
| Anxiety severity, mean BAI score (SD)                  | 4.0 (4.9)                   | 7.1 (6.5)                                    | 14.8 (9.4)            | 12.2 (8.8)                 | 21.2 (11.2)                                   | <0.001  |
| Severity of fear, mean FQ score                        | 0.8 (0.9)                   | 1.1 (0.9)                                    | 2.1 (1.2)             | 1.5 (1.2)                  | 2.6 (1.4)                                     | <0.001  |
| Severity of worry, mean PSWQ score (SD)                | 19.2 (9.9)                  | 24.5 (12.2)                                  | 29.8 (14.3)           | 29.6 (15.5)                | 33.0 (17.8)                                   | <0.001  |
| Symptom duration % of time with symptoms (months with) | NA                          | 21.7%                                        | 44.8%                 | 33.3%                      | 51.8%                                         | <0.001  |
| Age of onset (years), mean (SD)                        | NA                          | 26.1 (13.0)                                  | 19.3 (12.6)           | 25.5 (13.1)                | 19.6 (12.1)                                   | <0.001  |
| <b>Antidepressant use (%)</b>                          |                             |                                              |                       |                            |                                               |         |
| SSRI                                                   | 0.6%                        | 10.1%                                        | 19.1%                 | 23.7%                      | 32.1%                                         | <0.001  |
| TCA                                                    | 0.2%                        | 1.6%                                         | 3.7%                  | 2.8%                       | 4.8%                                          | <0.001  |
| Other                                                  | 0.2%                        | 1.1%                                         | 6.1%                  | 10.2%                      | 11.6%                                         | <0.001  |
| Psychotherapy (%)                                      | 3.8%                        | 6.6%                                         | 17.8%                 | 29.5%                      | 32.4%                                         | <0.001  |

Chi-square values have been computed for categorical variables, ANOVA for interval variables. Independent samples Kruskal-Wallis test were used for non-parametric variables.

Table 2: Adjusted mean scores for social functioning indicators across psychopathology with effect sizes (Cohen's d)\*

|                                        | Control subjects<br>N = 650 | Remitted anxiety or depression<br>N = 621 | Effect size | Pure Anxiety<br>N=540 | Effect size | Pure Depression<br>N=393 | Effect size | Comorbid anxiety and depression<br>N=748 | p-value | Differences***    |
|----------------------------------------|-----------------------------|-------------------------------------------|-------------|-----------------------|-------------|--------------------------|-------------|------------------------------------------|---------|-------------------|
| <b>Social behavioral indicators</b>    |                             |                                           |             |                       |             |                          |             |                                          |         |                   |
| Network size, mean category (SD)       | 3.2 (1.2)                   | 2.9 (1.1)**                               | 0.26        | 2.7 (1.1)**           | 0.43        | 2.6 (1.0)**              | 0.54        | 2.3 (1.0)**                              | <0.001  | 1>2=3>4>5         |
| Social activities, mean (SD)           | 14.8 (4.0)                  | 14.2 (4.2)                                |             | 13.6 (4.2)**          | 0.29        | 12.7 (4.4)**             | 0.50        | 11.6 (4.2)**                             | <0.001  | 1=2>3>4>5         |
| Social support, mean (SD)              | 29.8 (11.4)                 | 28.6 (11.4)**                             | 0.11        | 27.9 (12.3)**         | 0.16        | 27.4 (12.6)*             | 0.20        | 25.3 (12.6)**                            | <0.001  | 1>2=3=4>5         |
| <b>Social affective indicators</b>     |                             |                                           |             |                       |             |                          |             |                                          |         |                   |
| Loneliness, mean (SD)                  | 2.0 (2.6)                   | 3.3 (3.2)**                               | 0.45        | 4.9 (3.5)**           | 0.94        | 5.5 (3.6)**              | 1.11        | 6.7 (3.5)**                              | <0.001  | 1>2>3>4>5         |
| Affiliation, mean (SD)                 | 4.7 (1.6)                   | 4.7 (1.5)                                 |             | 4.5 (1.6)**           | 0.13        | 4.3 (1.6)**              | 0.25        | 4.1 (1.7)**                              | <0.001  | 1=2>3>5; 3=4; 4=5 |
| Perceived social disability, mean (SD) | 7.0 (2.8)                   | 8.4 (3.4)**                               | 0.45        | 10.5 (4.1)**          | 1.00        | 11.4 (4.4)**             | 1.19        | 13.7 (4.6)**                             | <0.001  | 1>2>3>4>5         |

Based on analyses table 1: adjusted for age, sex, educational level, partner status

\* as compared to control subjects

\*\* significant at p<0.05 level as compared to control subjects

\*\*\* significant differences between control subjects (1), remitted anxiety or depression patients (2), pure anxiety patients (3), pure depression patients (4) and comorbid anxiety and depression patients (5)

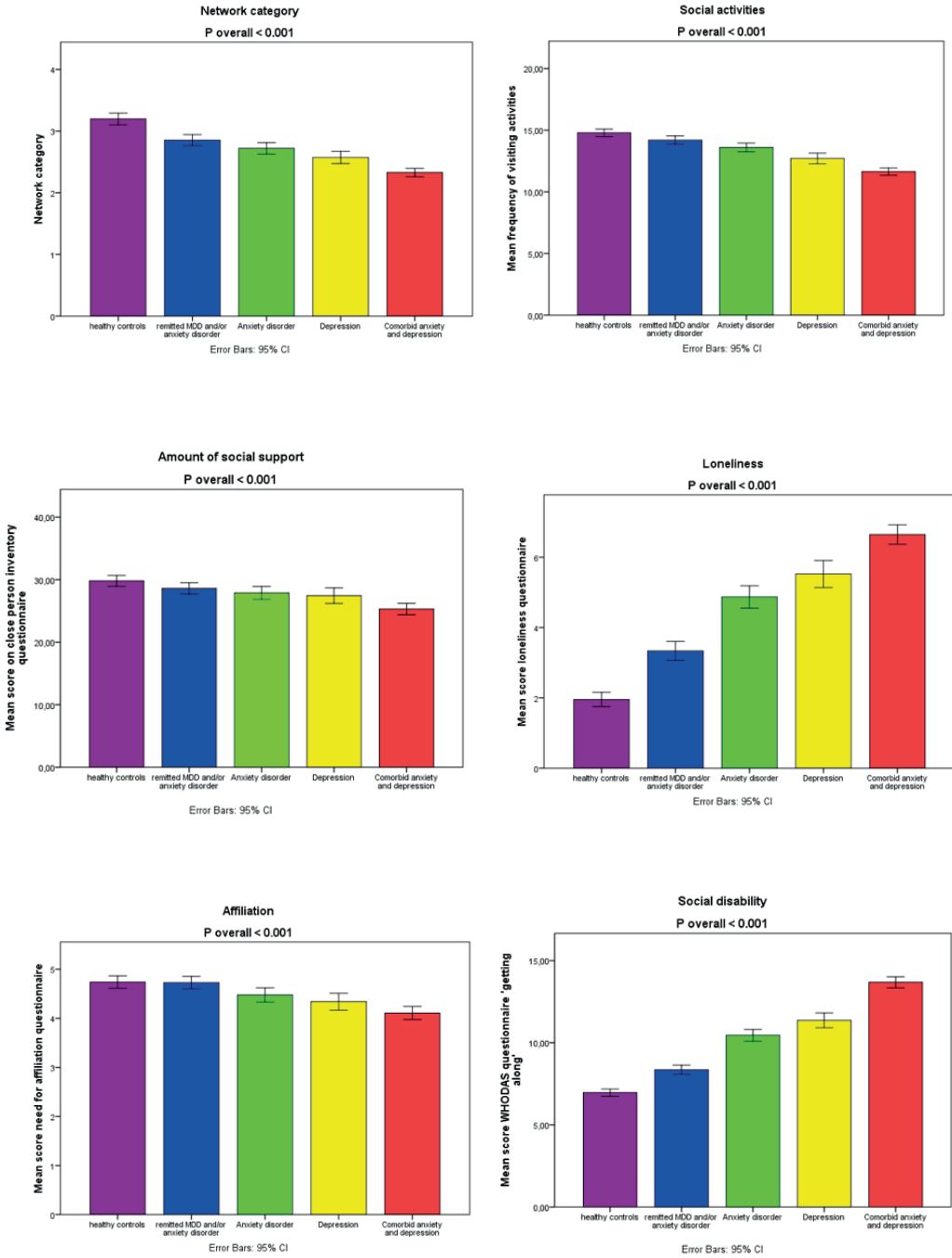


Figure 1: Means for social behavioral and social affective indicators across psychopathology, not adjusted for age, sex, education and partner status. Error bars represent the standard error. Y axis depicts the different scores.

Next, regression analyses (Table 3) examined how dimensional and categorical measures of psychopathology relate to social functioning indicators within the subgroup of patients with current affective disorder (N=1681), all adjusted for age, sex, education and partner status. In the first model, comorbid anxiety and depression related to more severe impairments on all indicators of social functioning, when contrasted to pure anxiety (reference) ( $\beta=0.343$ ,  $p<0.001$  for perceived social disability). Pure depression similarly related to more severe impairments in social functioning when contrasted to pure anxiety ( $\beta=0.081$ ,  $p<0.01$  for perceived social disability), with exception of social support and affiliation. Subsequently, we explored whether different depressive or anxiety disorders similarly impact social functioning (Table 3). Overall, of the specific types of disorders, MDD and SP seemed to impact social functioning most (network size SP:  $\beta=-0.098$ ,  $p<0.001$ ; MDD:  $\beta=-0.097$ ,  $p<0.001$ ; loneliness SP:  $\beta=0.100$ ,  $p<0.001$ ; MDD:  $\beta=-0.136$ ,  $p<0.001$ ; perceived social disability SP:  $\beta=0.306$ ,  $p<0.001$ ; MDD:  $\beta=0.247$ ,  $p<0.001$ ), followed by GAD, and dysthymia, with network size (GAD:  $\beta=-0.052$ ,  $p<0.05$ ; dysthymia:  $\beta=-0.076$ ,  $p<0.01$ ), loneliness (GAD:  $\beta=0.072$ ,  $p<0.01$ ; dysthymia:  $\beta=-0.119$ ,  $p<0.001$ ) and perceived social disability (GAD:  $\beta=0.077$ ,  $p<0.001$ ; dysthymia:  $\beta=0.133$ ,  $p<0.001$ ). PD and AP were not associated with social functioning indicators in these analyses, in which shared variance between disorder types was eliminated.

The third model assessed the association between dimensional measures of psychopathology and social functioning (Table 3). Overall, more severe depressive or anxiety symptomatology related to more impairment in social functioning. Depression severity was more strongly associated than anxiety severity with social functioning indicators. Severity of worrying was not significantly associated with social behavioral indicators, but highly associated with all affective indicators. Longer symptom duration was strongly associated with more unfavorable scoring on almost all social functioning indicators, except for social activities and affiliation. Lastly, a younger age of onset was associated with a smaller network size and all affective indicators ( $p's<0.01$ , except for affiliation  $p<0.05$ ). Loneliness and perceived social disability were negatively associated with all clinical characteristics.

Finally, we examined whether any of the social indicators was predictive for having a depressive or anxiety disorder two years later, using the clinical subsample of patients from the baseline with two-year follow-up data (N=1409). Overall, 47% of the sample still had a diagnosis of anxiety or depressive disorder after 2 years. For low social activities (Odds ratio 0.97 (0.94-1.00),  $p=0.06$ , Table 4) and high loneliness (Odds ratio 1.04 (1.00-1.08),  $p=0.07$ , Table 4) non-significant trends were visible when unadjusted for severity of depression and anxiety but adjusted for age, sex, years of education and partner status. Higher perceived social disability predicted a higher risk of still having

a disorder two years later, both adjusted for sex, age, education, partner status and severity of anxiety and depression, (Odds ratio respectively 1.10 (1.07-1.14),  $p<0.001$ , 1.05 (1.01-1.08),  $p<0.01$ , Table 4).

Table 3: Adjusted\* associations of clinical characteristics and various social functioning indicators\* within the group of current patients (N=1681)

|                        | Social behavioral indicators |                   |                | Social affective indicators |             |                             |
|------------------------|------------------------------|-------------------|----------------|-----------------------------|-------------|-----------------------------|
|                        | Network size                 | Social activities | Social support | Loneliness                  | Affiliation | Perceived social disability |
|                        | $\beta$                      | $\beta$           | B              | B                           | $\beta$     | $\beta$                     |
| Model 1:               |                              |                   |                |                             |             |                             |
| Pure anxiety           | Ref                          | Ref               | Ref            | Ref                         | Ref         | ref                         |
| Pure depression        | -0.062*                      | -0.095***         | -0.012         | 0.072**                     | -0.038      | 0.081**                     |
| Comorbid               | -0.174***                    | -0.189***         | -0.084**       | 0.227***                    | -0.097***   | 0.343***                    |
| Model 2:               |                              |                   |                |                             |             |                             |
| - Panic disorder       | 0.020                        | -0.020            | -0.015         | -0.032                      | -0.020      | -0.007                      |
| - GAD                  | -0.052*                      | -0.033            | -0.034         | 0.072**                     | -0.003      | 0.077***                    |
| - Social phobia        | -0.098***                    | -0.062**          | -0.048*        | 0.100***                    | -0.100***   | 0.306***                    |
| - Agoraphobia          | 0.034                        | -0.030            | -0.012         | 0.001                       | -0.018      | 0.032                       |
| - MDD                  | -0.097***                    | -0.128***         | -0.052*        | 0.136***                    | -0.088***   | 0.247***                    |
| - dysthymia            | -0.076**                     | -0.139***         | -0.067**       | 0.119***                    | -0.035      | 0.133***                    |
| Model 3:               |                              |                   |                |                             |             |                             |
| Severity of depression | -0.224***                    | -0.255***         | -0.143***      | 0.374***                    | -0.181***   | 0.599***                    |
| Severity of anxiety    | -0.090***                    | -0.176***         | -0.054*        | 0.207***                    | -0.117***   | 0.382***                    |
| Severity of fear       | -0.124***                    | -0.160***         | -0.061*        | 0.231***                    | -0.126***   | 0.438***                    |
| Severity of worrying   | -0.027                       | -0.023            | 0.034          | 0.256***                    | -0.079**    | 0.131***                    |
| Symptom duration       | -0.091***                    | -0.051*           | -0.071***      | 0.135***                    | -0.027      | 0.152***                    |
| Age of onset           | 0.100***                     | 0.037             | 0.024          | -0.162***                   | 0.058*      | -0.236***                   |

\* Adjusted for sex, age, educational level and partner status  
\* significant at  $p<0.05$  level; \*\*significant at  $p<0.01$ ; \*\*\* significant at  $p<0.001$

**Table 4: Logistic regression analyses predicting still having a depression and/or anxiety disorders at 2 year follow up in persons with a current baseline disorder (N=1409)**

|                                     | basic adjusted*<br>Odds ratio (95% CI),<br>P-value | adjusted for severity of<br>depression and anxiety**<br>Odds ratio (95% CI), P-value |
|-------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------|
| <b>Social behavioral indicators</b> |                                                    |                                                                                      |
| Network size                        | 1.04 (0.91-1.19), 0.56                             | 1.01 (0.88-1.15), 0.91                                                               |
| Social activities                   | 0.97 (0.94-1.00), 0.06                             | 0.98 (0.95-1.02), 0.28                                                               |
| Social support                      | 1.00 (1.00-1.00), 0.86                             | 1.00 (1.00-1.00), 0.76                                                               |
| <b>Social affective indicators</b>  |                                                    |                                                                                      |
| Loneliness                          | 1.04 (1.00-1.08), 0.07                             | 1.01 (0.97-1.06), 0.51                                                               |
| Affiliation                         | 0.97 (0.90-1.05), 0.50                             | 0.99 (0.92-1.08), 0.85                                                               |
| Perceived social disability         | 1.10 (1.07-1.14), p<.001                           | 1.05 (1.01-1.08), p<0.01                                                             |

\* corrected for age, sex, years of education, partner status

\*\* corrected for age, sex, years of education, partner status, severity of depression (IDS), severity of anxiety (BAI)

DISCUSSION

This comprehensive study of affective and behavioral indicators of social functioning found strong associations with depressive and anxiety disorders in a large naturalistic cohort. The findings indicate that social functioning is affected in patients with anxiety, even more so in those with depressive disorders, and most prominently in patients with comorbid anxiety and depression. Overall, affective aspects of social functioning seemed more hampered than behavioral ones. Interestingly, even after complete remission of affective psychopathology, residual impairments in social functioning exist, while social dysfunction in patients was predictive of future psychopathology. To our knowledge, no previous study has examined social functioning within a large sample comprising anxious, depressed, comorbid, remitted patients and healthy controls.

Our study clearly indicates both affective and behavioral aspects of social functioning are affected in patients with depressive and/or anxiety disorders, with affective aspects being most severely impaired. These findings are in line with two prior studies that combined both behavioral and affective indicators of social functioning in relation to physical and psychological well-being.<sup>6,33</sup> Rico-Uribe et al.<sup>33</sup> showed that loneliness was the strongest contributor to diminished physical health in comparison to network size, frequency of contact, and quality of social network. Santini et al.<sup>6</sup> described in a review that perceived support is more important in depressive disorders than received support. Our findings of impairments of

behavioral aspects are in agreement with the findings of a prior study showing that the absence of close friends and relatives is associated with increased risk of clinical anxiety and depression.<sup>34</sup>

We found that remitted patients differed significantly from healthy controls in network size, social support, loneliness and perceived social disability. This is in line with earlier findings <sup>35-37</sup> showing that social functioning remains impaired in remitted depressed participants. Stout et al.<sup>22</sup> also described that social functioning levels remain impaired for up to 18 months following remission from panic disorder. This impaired social functioning following remission can be the result of residual cognitive of affective symptoms or ‘social scarring’. However, such impaired social functioning can also be reflective of a vulnerability towards development of affective disorders, as was recently described by Schopman et al.<sup>38</sup> for anxiety disorders and by Ormel et al<sup>39</sup> and Pappmeyer et al.,<sup>40</sup> for depression. Longitudinal studies have tried to disentangle these different causal routes, and have found evidence for both routes.<sup>22,38-40</sup>

Although impairment of social functioning seemed generally more prominent in depressive disorders than in anxiety disorders, the largest effect sizes were found in patients with comorbid anxiety and depression. These results support previous data comparing psychosocial functioning in pure anxiety or depressive disorders <sup>17,41</sup> and their comorbidity.<sup>42</sup> With regard to specific anxiety disorders, we found that GAD and especially SP are more strongly associated with social dysfunction or higher impairment compared to PD and AP, which is in agreement with findings of several other studies.<sup>9,34,43</sup> Some authors suggest that GAD resembles MDD when it comes to social impairment,<sup>43</sup> while others opine that SP perturbs social functioning more strongly than many other psychiatric disorders.<sup>44</sup> In our study, we found no differences in social functioning between SP, MDD and dysthymia, although overall the effect sizes in MDD were larger than those of anxiety disorders. Remarkably, McKnight et al.<sup>10</sup> described in their review a significantly lower correlation between social functioning impairment and SP, compared to the other anxiety disorders. This contrasts the findings reported here, as well as those documented previously,<sup>5,9,20,44</sup> which indicate that SP involves more severe impairments on all social functioning indicators, as compared to other anxiety disorders.

The current study also found that high perceived social disability was predictive of clinical anxiety or depression two years later. Evidence suggests that residual psychosocial impairment increases the recurrence of depressive and anxious symptomatology,<sup>43,45</sup> and the affective components are suggested to drive this effect. Several studies have for instance shown that loneliness is predictive of both

depressive symptomatology within geriatric populations<sup>8,46,47</sup> and social phobia.<sup>48</sup> Yet, in our analyses, loneliness was not predictive of future psychopathology, with perceived social disability emerging as the sole significant predictor of anxiety and/or depressive disorders two years after the initial screening. Despite this apparent discrepancy, our results do further implicate impaired affective social functioning as a strong predictor of future psychopathology. Of note, this analysis implicates that disability contributes to subsequent psychopathology course. This possible pre-existent vulnerability for psychopathology has been described by others.<sup>38–40</sup> Although this was not addressed in our study, it is likely that there is also a reversed link, i.e., a longitudinal impact of psychopathology on subsequent social functioning.

As described, impaired social functioning is highly associated with anxious and depressive symptomatology, although the underlying pathophysiological mechanisms remain largely elusive.<sup>49,50</sup> One possible explanation is that social interactions might be appreciated as less rewarding in anxious or depressed patients, due to impaired signaling of brain's reward system, in which the amygdala is crucially implicated.<sup>51</sup> This inability to gain reward from social interactions may lead to anhedonia symptoms.<sup>49</sup> Future studies focusing specifically on the 'social brain', including the social reward system, could greatly advance our understanding of the underlying pathomechanisms of impaired social functioning.

The current study is unique in its large size and its comparison of different patient groups and characteristics in relationship to social functioning. Some limitations, however, need to be discussed as well. First, most of our analyses were cross-sectional, thereby not allowing causal inferences. Also, more detailed aspects of social functioning, such as the exact composition of the social network were not examined in our study. Differences between our findings and previous findings might stem from the use of different measures of symptomatology and social functioning. In addition, cognitive biases associated with depression or anxiety may have influenced the patient's response and thus their reported social function. Ideally, we would have used actual behavioral data, instead of retrospective self-reports. An interesting new development is the use of tools like ecological momentary assessment, which allows obtaining real-time information about social activities of patients and their affective state.

In summary, the current study reveals that social functioning is affected in patients with anxiety, even more so in those with depressive disorders, and most prominently in patients with comorbid disorders. Interestingly, even after complete remission of affective psychopathology residual impairments of social functioning exist, which might indicate possible 'social scarring' or preexisting vulnerability factors, with

perceived social disability in patients additionally predicting future psychopathology. As social impairments are one of the earliest presenting symptoms in a wide variety of psychopathologies, future studies should aim to disentangle common and specific (biological) characteristics of social functioning using a trans-diagnostic approach.

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## Cross-Disorder and Disorder-Specific Deficits in Social Functioning Among Schizophrenia and Alzheimer's Disease Patients

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ABSTRACT

**BACKGROUND** Social functioning is often impaired in schizophrenia (SZ) and Alzheimer’s disease (AD). However, commonalities and differences in social dysfunction among these patient groups remain elusive.

**METHODS** Using data from the PRISM study, behavioral (all subscales and total score of the Social Functioning Scale) and affective (perceived social disability and loneliness) indicators of social functioning were measured in patients with SZ (N=56), probable AD (N=50) and age-matched healthy controls groups (HC, N=29 and N=28). We examined to what extent social functioning differed between disease and age-matched HC groups, as well as between patient groups. Furthermore, we examined how severity of disease and mood were correlated with social functioning, irrespective of diagnosis.

**RESULTS** As compared to HC, both behavioral and affective social functioning seemed impaired in SZ patients (Cohen’s *d*’s 0.81-1.69), whereas AD patients mainly showed impaired behavioral social function (Cohen’s *d*’s 0.65-1.14). While behavioral indices of social functioning were similar across patient groups, SZ patients reported more perceived social disability than AD patients (Cohen’s *d*’s 0.65). Across patient groups, positive mood, lower depression and anxiety levels were strong determinants of better social functioning (*p*’s <0.001), even more so than severity of disease.

**CONCLUSIONS** AD and SZ patients both exhibit poor social functioning in comparison to age- and sex matched HC participants. Social dysfunction in SZ patients may be more severe than in AD patients, though this may be due to underreporting by AD patients. Across patients, social functioning appeared as more influenced by mood states than by severity of disease.

Highlights

- 1. SZ and AD patients both exhibit poor social functioning in comparison to age- and sex matched controls.
- 2. Social dysfunction is more severe in SZ patients than in AD patients, though this could be partly due to underreporting by AD patients.
- 3. Social functioning in SZ and AD is influenced more by mood state than by severity of disease.

## INTRODUCTION

Social functioning is crucial for human survival and it has been established that 'loneliness kills'.<sup>1,2</sup> Social functioning entails a collection of intricate and multifactorial behavioral repertoires, which seem to be facilitated by many complex brain network processes.<sup>3-5</sup> Because of its complexity, social dysfunction often arises as one of the first symptoms in neuropsychiatric disorders such as Schizophrenia (SZ) and Alzheimer's disease (AD).<sup>3</sup> However, the origins of social dysfunction in these disorders remain poorly understood.<sup>6,7</sup> Specifically, while SZ and AD patients are characterized by distinctive psychopathologies, their psychosocial deficits are deemed partly overlapping. However, empirical data on behavioral and neurobiological commonalities and differences is practically lacking.

The definition of 'social dysfunction' has specific focal points dependent on the disorder being studied, with a broad range in study methods and outcome measures as a consequence. Social dysfunction in SZ is described in a large and growing body of literature that has identified severe impairments in mentalizing, interpersonal interaction, regulating emotions and emotion decoding in social situations.<sup>8-11</sup> It has been argued that higher order social processes such as mentalizing are more prone to deficits in SZ patients than processes which require less mental effort, such as emotion recognition and mirroring.<sup>8,12</sup> In addition, social withdrawal is described as a prodromal symptom of SZ, with an onset up to several years before the first psychotic episode.<sup>13</sup> In contrast to SZ, empirical data on social dysfunction in AD is arguably more sparse. Social dysfunction in AD typically starts with initially subtle impairments in social and affective cognition, which worsen as the disorder progresses.<sup>14,15</sup> Social impairment has been described as a distinct constellation of AD symptoms, possibly explained by the degenerative processes differentially affecting brain regions.<sup>16</sup> More specifically, in AD social dysfunction seems to be associated with impairments in interpreting cues to others' emotional states, and thus identifying others' emotions.<sup>15</sup> In addition, it has been described that the judgments of AD patients about their own social functioning is more positive than according to the perception of the caregiver.<sup>14,17,18</sup> In sum, social functioning in both SZ and AD seems most affected in understanding others.<sup>7</sup>

The notion of highly overlapping social functioning deficits in neuropsychiatric disorders has gained more support and interest in recent years, especially since the launch of the RDoC framework and the EU-ROAMER initiatives, which advocate a deeper understanding of trans-diagnostic clinical phenomena and their neurobiobehavioral underpinnings.<sup>19,20</sup> However, before being able to examine such

underpinnings, it is necessary to more fully grasp the differences and commonalities in a complex phenomenon such as social dysfunction – including both behavioral and affective aspects - across neuropsychiatric disorders.

The main aim of the present study is to examine differences and commonalities in affective and behavioral indicators of social functioning among SZ and AD patients, and age and sex-matched healthy controls (HC), which could ultimately guide future neurobiological research on the topic. The current study is part of the larger EU-funded PRISM Project (Psychiatric Ratings using Intermediate Stratified Markers), which examines the neurobiobehavioral underpinnings of social dysfunction in order to advance and formulate more effective treatment strategies.<sup>21</sup> SZ and AD were chosen because of their overlapping social function deficits, in the face of distinctive psychopathologies and disorder characteristics (i.e. the obvious age difference).<sup>21</sup> We aimed to include patients with a relatively recent disease onset to capture as much as possible the underlying neurobiology of *social dysfunction* rather than long-term consequences of psychopathology or neurodegeneration. A transdiagnostic approach of investigating social (dys)function with these two discrete clinical entities may thus elucidate both disorder-specific and cross-disorder deficits.

## MATERIAL AND METHODS

### Participants

Data for the current study were derived from the PRISM study, which examines social dysfunction as a transdiagnostic symptom in individuals with SZ (N=56), probable AD (N=52), and age-matched HC participants (two groups, N=29 for younger HC (age 18-45) and N=28 for older HC (age 50-80)).<sup>21</sup> Two participants (AD patients) did not complete social functioning questionnaires, leaving 163 participants for analyses.

Participants were recruited between July 2017 and March 2019 from five different recruiting sites across Spain (Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa) and the Netherlands (University Medical Center Utrecht, VU University Medical Center Amsterdam and Leiden University Medical Center). The study was approved by the Ethics Review Board of corresponding countries and by local review boards of all participating centers. All participants provided verbal and written informed consent. Rationale and clinical implementation for the PRISM study is described in depth elsewhere.<sup>4,21,22</sup>

### In- and exclusion criteria

SZ patients were eligible if they had a) a diagnosis of schizophrenia (confirmed using DSM-based Mini-International Neuropsychiatric Interview (MINI) assessment), b) had a maximum of 15-year disease duration since diagnosis, c) an age between 18-45 years, and d) a score of  $\leq 22$  on the 7-item positive subscale of the positive and negative syndrome scale (PANSS)<sup>23</sup> to rule out an active psychotic episode hampering adequate study participation.<sup>22</sup> SZ patients were excluded when they were, in the clinician's judgment, a danger to themselves or others. AD patients were eligible if they had: a) a diagnosis of probable AD (meeting the National Institute on Aging and the Alzheimer's Association criteria), b) a Mini-Mental State Examination (MMSE)<sup>24</sup> score between 20-26 (indicating mild AD pathology), c) an aged between 50-80 years. Multiple strokes, either based on clinical judgement, medical history or imaging results were exclusion criteria for the AD patient group.

For both the SZ and AD patient groups, we had additional exclusion criteria: a) diagnosis of a severe, current Major Depressive Disorder (MDD) DSM-IV diagnosis (as assessed with the MINI)<sup>25</sup> and with a Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR)<sup>26</sup>  $\geq 16$ , b) diagnosis of any other *primary* psychiatric diagnosis that requires intervention; c) alcohol or drug abuse/dependence within previous 3 years (as assessed on the MINI), d) severe Parkinsonism as a consequence of antipsychotic medication (as assessed with a score  $\geq 4$  on the Extrapyramidal Symptom Rating Scale)<sup>27</sup>, e) unstable comorbid somatic disorders potentially affecting the central nervous system (CNS), f) unstable use of medication that could affect CNS (e.g. start of or changed dosage within last 8 weeks).

We included two HC groups, matching on sex and age with the SZ (between 18-45 years) and AD (between 50-80 years) groups. Scores on the MMSE for the older HC participants should be comparable to normative data according to age and years of education. Exclusion criteria for the HC groups were: a) history of psychiatric Axis-I disorder (as confirmed by the MINI) or neurological disease associated with cognitive impairment; b) mild or more severe depression (score  $>5$  on the QIDS-SR); c) current or prior use of antidepressant or anxiolytic medication including benzodiazepines, or other prescribed medication in the last 6 weeks that may affect the CNS.

### Behavioral and affective social functioning indicators

The neurobiological underpinnings of the subjective, affective evaluation of social interactions (i.e. loneliness, self-perceived social capacities) are thought to differ from the ones underlying the more objective, behavioral aspects of social interactions (i.e.

frequency of participating in social activities, hours spend alone).<sup>4,28,29</sup> We therefore differentiate between behavioral and affective indicators of social functioning, in line with prior work by our group.<sup>28</sup>

**Behavioral indicators of social functioning** - The Social Functioning Scale (SFS) consists of seven subscales; social withdrawal, interpersonal functioning, competence and performance independence, recreational and prosocial activities, and employment. The subscale 'employment' was not used for total scale analyses, since most participants were retired in the older HC and AD group introducing a bias as confirmed by the significant association with age and in line with reporting in a previous study.<sup>30</sup> We conducted Principal Component Analyses with oblique rotation as the variables are correlated to test if the different subscales represent one factor (i.e. behavioral social functioning) or two (i.e. affective and behavioral aspects of social functioning). In line with other studies using the SFS<sup>30-32</sup>, the factor analysis confirmed that the six SFS subscales reflect one component (see supplement 1). The social withdrawal subscale (higher score indicates less social withdrawal) focuses on time spend alone. The interpersonal functioning subscale includes ability to have rational conversation and difficulty talking to people. The subscale independence-competence and independence-performance are two identical lists of activities (e.g. buying items from shops alone) where participants judge whether they *think* they are able to do these independently (competence) and following what they actually independently *did* in the past three months (performance). The subscales, recreational and pro-social activities, consist of a list with several activities such as visiting relatives or playing sports, and the frequency in which participants engage in that activity. We followed the original SFS scoring guidelines with provided conversion table for the total SFS score and raw sum score on the subscales since standardization was calculated for a SZ population. For completeness we also included scaled scores for the subscales unadjusted for covariates (supplement 2).<sup>31</sup>

**Affective indicators of social functioning** - Loneliness was assessed with the 11-item de Jong Gierveld loneliness scale<sup>33</sup>, which examines feelings of loneliness. Perceived social disability was measured with an adjusted 5-item 'getting along' subdomain from the WHODAS 2.0 (WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0<sup>34</sup>), which includes questions about difficulties in maintaining friendships in the last 30 days.<sup>4,34</sup> Our division of social dysfunction (behavioral versus affective) is supported by higher inter-domain than cross-domain correlations between behavioral and affective social indicators (see Table 2).

For patients, perceived social disability (WHO-DAS 2.0) was also assessed by the caregiver when available (most often parent or partner) and by the research staff conducting the assessment. Consistent with our earlier observations,<sup>35</sup> correlations between the caregiver and researcher rated scores were high ( $r=.79$  for SZ group;  $r=.79$  for AD group, both  $p's < 0.001$ , see also Supplement 3) and there were some missing values (not all patients participated in the study with a caregiver). In cases where both scores were available, we computed a 'rater-perceived' social disability score by calculating a mean score from both the caregiver and researcher rated score. In other cases, we used the available score (either caregiver or researcher rated). Correlations were strong for the SZ and HC groups between their self-rated perceived social disability score and the rater score ( $r=.84$  for SZ;  $r=.90$  for HC,  $p's < 0.001$ ). For AD patients the correlation between the self-rated and rater-score was lower ( $r=.36$ ). Corresponding to our earlier study on the self- and proxy-rated WHODAS scores<sup>35</sup>, caregiver/researcher rated perceived social disability was higher than the rating by the AD patients themselves. We included the rater-perceived social disability in our analyses comparing patient groups.

### Severity of disease

Cognitive dysfunction was estimated in AD patients using the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog)<sup>36</sup> which includes 13 tasks involving both subject-completed test and observer-based assessments such as word recall, naming objects, and orientation. Current states of positive and negative symptoms of schizophrenia were measured using the PANSS (positive and negative syndrome scale)<sup>23</sup>.

### Mood characteristics

All participants (patients and controls) were asked to complete three mood questionnaires. The 16-item Quick inventory of Depressive Symptomatology (QIDS-SR)<sup>26</sup>, the 20-item State-Trait Anxiety Inventory (STAI)<sup>37</sup> and the 20-item Positive and Negative Affect Scale (PANAS)<sup>38</sup> examined depressive symptoms, anxiety symptoms and current positive and negative affect states, respectively.

### Statistical analyses

Demographic and clinical characteristics were described using  $\chi^2$  for dichotomous variables and t-tests for continuous variables. The Mann-Whitney test was used as nonparametric test when assumptions parametric testing were not met. Pearson correlations described associations between social functioning indicators and continuous demographics (age, years of education), point-biserial correlation coefficient described associations for binary demographics (sex, partner status and country). Analyses of covariance (ANCOVA's) with post-hoc tests, all Bonferroni

adjusted, compared social functioning indicators among SZ and AD patients, as well as their age-matched HC groups, while adjusting for age, sex, years of education, partner status and country. Effect sizes were calculated following Cohen's formula for estimated differences.<sup>39</sup> To examine the association of disease severity and mood (the dependent variables) with behavioral and affective indicators of social functioning (independent variables), linear regression analyses were conducted, again while adjusting for age, sex, years of education, partner status and country. Statistical analyses were conducted using SPSS (IBM, version 24.0, IBM Corp., Armonk, NY, USA), and a two-tailed significance level of  $P < 0.05$  was considered statistically significant.

## RESULTS

HC participants had most years of education (17.2 and 16.7 for younger and older HC respectively), whilst both of the patient groups had on average 15.0 years of education (see Table 1). SZ patients were less frequently with a partner (21.4%) as compared to younger HC (51.7%), AD patients (84.0%) and older HC (82.1%). As expected, psychotropic medication use was high in SZ patients (e.g. 89.3% used antipsychotics) and 43.8% of AD patients used acetylcholinesterase inhibitor and/or a NDMA receptor antagonist.

Current positive and negative symptoms among SZ patients were 11.0 (SD  $\pm 3.4$ ) and 14.6 (SD  $\pm 6.2$ ) respectively on the PANSS (mean total score 51, SD  $\pm 13.1$ ). Mean cognitive dysfunction of AD was 26.9 (SD  $\pm 7.2$ ) on the ADAS-COG. SZ participants had more negative mood symptoms (i.e. more depressed mood, more anxiety, less positive affect and more negative affect) than all other groups (AD and both HC groups). Anxiety and negative affect were comparable between AD and their matched HC group, but AD patients had more depressive symptomatology and less positive affect (see Table 1).

Correlation analyses (see Table 2) across all participants show that age, educational level and partner status had significant associations with almost all social indices. However, sex and country had much less consistent associations with social indices (up to three associations were significant but without consistent direction of association).

Table 1: Baseline characteristics (N=163) across patient and control groups

|                                                                |  | Schizophrenia patients<br>(N = 56) | Younger healthy controls<br>(N = 29) | p-value | Alzheimer's disease patients<br>(N=50) | Older healthy controls<br>(N =28) | p-value |
|----------------------------------------------------------------|--|------------------------------------|--------------------------------------|---------|----------------------------------------|-----------------------------------|---------|
| <b>Demographics</b>                                            |  |                                    |                                      |         |                                        |                                   |         |
| Age, mean years (SD)                                           |  | 30.8 (6.4)                         | 28.7 (7.4)                           | 0.13    | 68.6 (7.2)                             | 67.1 (7.0)                        | 0.32    |
| Sex (% female)                                                 |  | 28.6%                              | 41.4%                                | 0.23    | 44.0%                                  | 46.4%                             | 0.84    |
| Education, mean years (SD)                                     |  | 15.0 (3.8)                         | 17.2 (2.6)                           | 0.001   | 15.0 (5.6)                             | 16.7 (4.9)                        | 0.21    |
| Partner status (% with partner)                                |  | 21.4%                              | 51.7%                                | 0.004   | 84.0%                                  | 82.1%                             | 0.83    |
| Country (% Spain)                                              |  | 39.1%                              | 48.3%                                | 0.43    | 42.0%                                  | 25.0%                             | 0.13    |
| <b>Specific disorder characteristics</b>                       |  |                                    |                                      |         |                                        |                                   |         |
| <b>Psychotropic medication</b>                                 |  |                                    |                                      |         |                                        |                                   |         |
| Antipsychotic (%)                                              |  | 89.3%                              | 0%                                   |         | 4.0%                                   | 0%                                |         |
| Antidepressant (%)                                             |  | 19.6%                              | 0%                                   |         | 16.0%                                  | 0%                                |         |
| Acetylcholinesterase inhibitor or NDMA receptor antagonist (%) |  | 0%                                 | 0%                                   |         | 43.8%                                  | 0%                                |         |
| Benzodiazepines (%)                                            |  | 10.7%                              | 0%                                   |         | 6.3%                                   | 7.1%                              |         |
| Other psychotropics (%)                                        |  | 14.3%                              | 0%                                   |         | 2.1%                                   | 3.6%                              |         |
| <b>Severity of disorder</b>                                    |  |                                    |                                      |         |                                        |                                   |         |
| Schizophrenia severity                                         |  |                                    | NA                                   |         | NA                                     | NA                                |         |
| Positive symptoms, mean PANSS (SD)                             |  | 11.0 (3.4)                         |                                      |         |                                        |                                   |         |
| Negative symptoms, mean PANSS (SD)                             |  | 14.6 (6.2)                         | NA                                   |         | NA                                     | NA                                |         |
| AD severity, mean ADAS-Cog (SD)                                |  | NA                                 | NA                                   |         | 26.9 (7.2)                             | NA                                |         |
| <b>Mood characteristics</b>                                    |  |                                    |                                      |         |                                        |                                   |         |
| Depression severity, mean QIDS-SR (SD)                         |  | 8.0 (5.3)                          | 2.1 (1.5)                            | <0.001  | 4.1 (2.8)                              | 2.0 (1.3)                         | <0.001  |
| Anxiety severity, mean STAI (SD)                               |  | 43.5 (11.2)                        | 30.4 (5.9)                           | <0.001  | 30.7 (8.2)                             | 27.5 (5.8)                        | 0.08    |
| Mood state, PANAS                                              |  |                                    |                                      |         |                                        |                                   |         |
| Positive Affect, mean (SD)                                     |  | 29.5 (6.6)                         | 37.5 (5.9)                           | <0.001  | 32.5 (5.1)                             | 38.2 (6.1)                        | <0.001  |
| Negative Affect, mean (SD)                                     |  | 18.7 (6.5)                         | 13.9 (3.0)                           | <0.001  | 13.9 (4.6)                             | 12.7 (3.0)                        | 0.24    |

Table 2: Pearson and point biserial correlations between social indicators and demographics in the overall sample (N=163)

|                                   |  | Behavioral social indicators |                           |                         |                          |                         |                      |                 | Affective social indicators |                                   |            |
|-----------------------------------|--|------------------------------|---------------------------|-------------------------|--------------------------|-------------------------|----------------------|-----------------|-----------------------------|-----------------------------------|------------|
|                                   |  | Social withdrawal            | Interpersonal functioning | Independence competence | Independence performance | Recreational activities | Prosocial activities | Total SFS score | Perceived social disability | Rater-perceived social disability | Loneliness |
| Demographics                      |  |                              |                           |                         |                          |                         |                      |                 |                             |                                   |            |
| Age                               |  | .273***                      | .272**                    | -.162*                  | -.060                    | .376**                  | .119                 | .229**          | -.305**                     | -.135                             | -.217**    |
| Sex (female=1; male=0)            |  | .160*                        | .036                      | -.009                   | .187*                    | .108                    | .028                 | .117            | -.032                       | -.060                             | -.057      |
| Education level                   |  | .148                         | .189*                     | .157*                   | .247**                   | .176*                   | .289**               | .272**          | -.071                       | -.261**                           | -.125      |
| Partner status (yes=1, no=0)      |  | .413**                       | .372**                    | .055                    | .012                     | .268**                  | .151                 | .332**          | -.382**                     | -.342**                           | -.356**    |
| Country (Spain=1; Netherlands=0)  |  | -.189*                       | -.120                     | -.161*                  | -.039                    | -.140                   | .027                 | -.160*          | -.013                       | .048                              | .201*      |
| Behavioral social indicators      |  |                              |                           |                         |                          |                         |                      |                 |                             |                                   |            |
| Social withdrawal                 |  | 1                            |                           |                         |                          |                         |                      |                 |                             |                                   |            |
| Interpersonal functioning         |  | .541**                       | 1                         |                         |                          |                         |                      |                 |                             |                                   |            |
| Independence-competence           |  | .256**                       | .320**                    | 1                       |                          |                         |                      |                 |                             |                                   |            |
| Independence-performance          |  | .283**                       | .361**                    | .605**                  | 1                        |                         |                      |                 |                             |                                   |            |
| Recreational activities           |  | .437**                       | .389**                    | .359**                  | .440**                   | 1                       |                      |                 |                             |                                   |            |
| Prosocial activities              |  | .465**                       | .482**                    | .343**                  | .492**                   | .564**                  | 1                    |                 |                             |                                   |            |
| Total SFS score                   |  | .715**                       | .763**                    | .595**                  | .671**                   | .749**                  | .755**               | 1               |                             |                                   |            |
| Affective social indicators       |  |                              |                           |                         |                          |                         |                      |                 |                             |                                   |            |
| Perceived social disability       |  | -.572**                      | -.681**                   | -.357**                 | -.307**                  | -.414**                 | -.504**              | -.662**         | 1                           |                                   |            |
| Rater-perceived social disability |  | -.560**                      | -.598**                   | -.434**                 | -.483**                  | -.496**                 | -.616**              | -.730**         | .785**                      | 1                                 |            |
| Loneliness                        |  | -.556**                      | -.615**                   | -.296**                 | -.278**                  | -.357**                 | -.393**              | -.594**         | .615**                      | .536**                            | 1          |

\* p-value < 0.05, \*\* p-value<0.01, \*\*\* p-value<0.001

### Comparison of patient groups with healthy controls

Figure 1 shows unadjusted means for the total SFS score as behavioral indicator, and self-rated perceived social disability and loneliness as affective social indicators per group with comparisons for SZ and AD with their age-matched controls. It is clear in Table 3 that the least favorable social functioning outcomes on all measures were found for the SZ group with large effect sizes (Cohen's  $d$ 's=0.81-1.69) particularly pronounced for the affective indicators. AD patients showed less favorable outcomes for most behavioral social functioning indicators as compared to their matched HC group: independence-competence and -performance, recreational and prosocial activities and the total SFS score with medium to large effect sizes ( $d$ 's=0.65-1.14). For both SZ and AD patients the total SFS was significantly lower from their age-matched controls with large effect sizes ( $d$ =1.80 and 1.14 respectively). Affective social functional indicators of perceived social disability and loneliness, however, were not significantly different ( $d$ 's=0.17 and  $d$ =0.05 respectively) between AD and older HC participants. In contrast, the (mean score of caregiver and research staff) rater-perceived social disability was significantly worse in AD as compared to the older HC group ( $p<0.001$ ,  $d$ =1.29).

### Comparisons across/within patient groups

In the cross-disorder comparison between SZ and AD patients, (Table 4), all behavioral social indicators were comparable, as well as the total SFS score ( $p=0.70$ ,  $d=0.31$ ). Perceived social disability showed a significantly poorer outcome for SZ patients as compared to AD participants (Cohen's  $d=0.65$ ,  $p=0.008$ ). The self-reported perceived social disability was higher in SZ compared to AD patients, but was not significantly different for the rater-perceived social disability.

Linear regression analyses (Table 5) examined the association between clinical characteristics (severity of disorder, mood, positive/negative affect) and social functioning indices among SZ and AD patients adjusted for aforementioned covariates. Overall, only a few predictors were found to associate strongly with overall disease severity. More AD symptomatology was associated with fewer prosocial activities ( $\beta=-0.400$ ,  $p=0.014$ ). More negative SZ symptomatology was associated with less interpersonal functioning ( $\beta=-0.330$ ,  $p=0.010$ ), and more positive SZ symptoms related to more loneliness ( $\beta=0.278$ ,  $p=0.049$ ). Disease severity was not associated with the total SFS.

More consistent associations were found for mood state indicators (Table 5). Across both diagnostic groups, positive affect was associated with all behavioral and affective social functioning indicators, except for independence-competence and -performance. More favorable social functioning was found for those with less

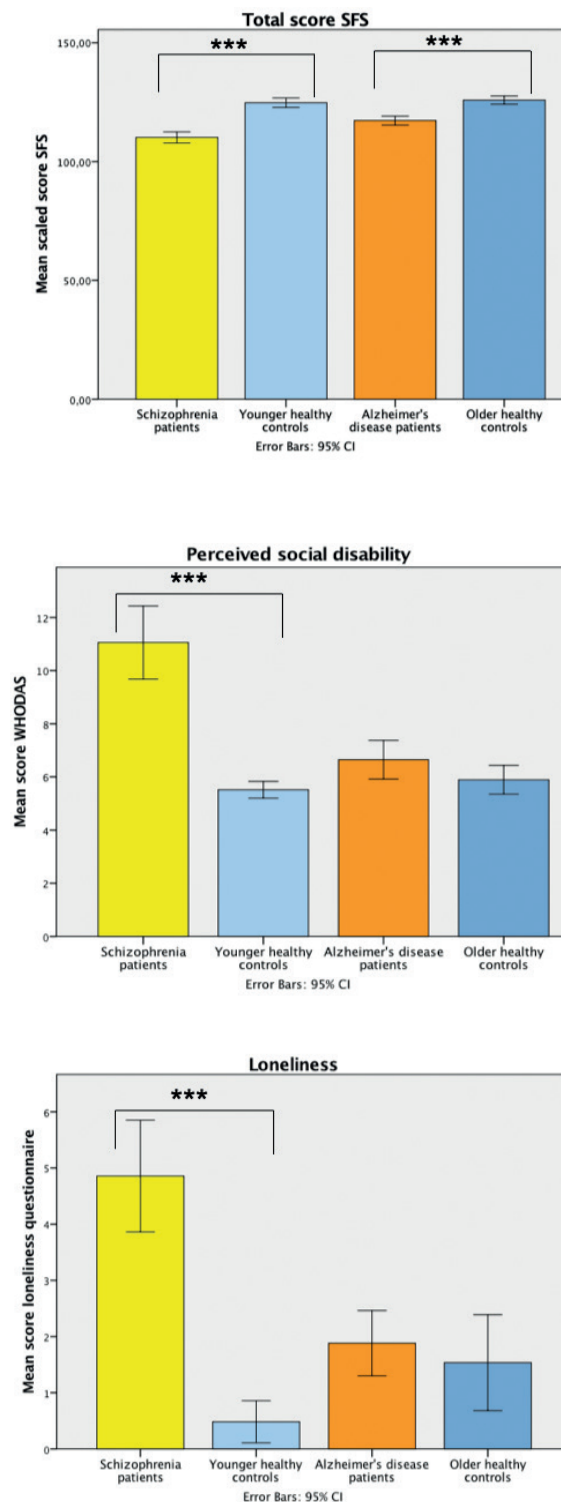


Figure 1: Unadjusted mean scores for total SFS, loneliness and perceived social disability across psychopathology. Error bars represent the standard error. Y axis depicts the different scores. \* $p$ -value < 0.05, \*\*  $p$ -value<0.01, \*\*\*  $p$ -value<0.001

Table 3: Mean adjusted<sup>†</sup> social functioning scores across disorders compared with healthy controls with effect sizes (N=163)

|                                                 | Schizophrenia patients<br>N = 56 | Younger healthy controls<br>N = 29 | p-value | Effect size<br>Cohen's <i>d</i> | Alzheimer's disease patients<br>N=50 | Older healthy controls<br>N= 28 | p-value | Effect size<br>Cohen's <i>d</i> |
|-------------------------------------------------|----------------------------------|------------------------------------|---------|---------------------------------|--------------------------------------|---------------------------------|---------|---------------------------------|
| <b>Behavioral social functioning indicators</b> |                                  |                                    |         |                                 |                                      |                                 |         |                                 |
| Social withdrawal, mean (SE)                    | 10.4 (0.5)                       | 13.3 (0.6)                         | <0.001  | 1.30                            | 12.3 (0.5)                           | 13.1 (0.6)                      | 0.74    | 0.35                            |
| Interpersonal functioning, mean (SE)            | 6.4 (0.4)                        | 8.5 (0.4)                          | <0.001  | 1.33                            | 8.1 (0.4)                            | 8.8 (0.4)                       | 0.43    | 0.66                            |
| Independence-competence, mean (SE)              | 36.2 (0.7)                       | 38.7 (0.8)                         | 0.002   | 0.81                            | 33.9 (0.8)                           | 37.0 (0.8)                      | <0.001  | 1.06                            |
| Independence-performance, mean (SE)             | 29.4 (1.1)                       | 34.6 (1.3)                         | <0.001  | 1.04                            | 28.1 (1.2)                           | 32.4 (1.3)                      | <0.001  | 0.96                            |
| Recreation activities, mean (SE)                | 19.3 (1.4)                       | 24.5 (1.7)                         | 0.002   | 0.81                            | 23.2 (1.6)                           | 28.3 (1.7)                      | 0.002   | 0.83                            |
| Prosocial activities, mean (SE)                 | 24.8 (2.1)                       | 36.8 (2.6)                         | <0.001  | 1.25                            | 28.6 (2.4)                           | 34.5 (2.5)                      | 0.030   | 0.65                            |
| Total SFS score, mean (SE)                      | 111.2 (1.7)                      | 125.3 (2.1)                        | <0.001  | 1.80                            | 116.5 (1.9)                          | 124.9 (2.0)                     | <0.001  | 1.14                            |
| <b>Affective social functioning indicators</b>  |                                  |                                    |         |                                 |                                      |                                 |         |                                 |
| Perceived social disability, mean (SE)          | 11.3 (0.8)                       | 6.1 (1.0)                          | <0.001  | 1.39                            | 6.1 (0.9)                            | 5.5 (1.0)                       | 1.00    | 0.17                            |
| Rater-perceived social disability, mean (SE)    | 12.2 (0.8)                       | 5.7 (1.0)                          | <0.001  | 1.69                            | 10.5 (1.0)                           | 6.0 (1.0)                       | <0.001  | 1.29                            |
| Loneliness, mean (SE)                           | 4.6 (0.6)                        | 0.4 (0.8)                          | <0.001  | 1.45                            | 2.0 (0.7)                            | 1.8 (0.8)                       | 1.00    | 0.05                            |

<sup>†</sup> Adjusted for age, sex, years of education, partner status and country. Bonferroni adjustment for multiple comparisons.

Table 4: Mean adjusted<sup>†</sup> social functioning scores across disorders with effect sizes (N=106)

|                                              | Schizophrenia patients<br>N = 56 | Alzheimer's disease patients<br>N=50 | p-value | Effect size<br><i>d</i> |
|----------------------------------------------|----------------------------------|--------------------------------------|---------|-------------------------|
| <b>Behavioral social indicators</b>          |                                  |                                      |         |                         |
| Social withdrawal, mean (SE)                 | 10.4 (0.5)                       | 12.3 (0.5)                           | 0.27    | 0.40                    |
| Interpersonal functioning, mean (SE)         | 6.4 (0.4)                        | 8.1 (0.4)                            | 0.08    | 0.28                    |
| Independence-competence, mean (SE)           | 36.2 (0.7)                       | 33.9 (0.8)                           | 0.54    | 0.33                    |
| Independence-performance, mean (SE)          | 29.4 (1.1)                       | 28.1 (1.2)                           | 1.00    | 0.13                    |
| Recreational activities, mean (SE)           | 19.3 (1.4)                       | 23.2 (1.6)                           | 0.98    | 0.27                    |
| Pro-social activities, mean (SE)             | 24.8 (2.1)                       | 28.6 (2.4)                           | 1.00    | 0.18                    |
| Total SFS score, mean (SE)                   | 111.2 (1.7)                      | 116.5 (1.9)                          | 0.70    | 0.31                    |
| <b>Affective social indicators</b>           |                                  |                                      |         |                         |
| Perceived social disability, mean (SE)       | 11.3 (0.8)                       | 6.1 (0.9)                            | 0.008   | 0.65                    |
| Rater-perceived social disability, mean (SE) | 12.2 (0.8)                       | 10.5 (1.0)                           | 1.00    | 0.20                    |
| Loneliness, mean (SE)                        | 4.6 (0.6)                        | 2.0 (0.7)                            | 0.21    | 0.41                    |

<sup>†</sup> Adjusted for age, sex, years of education, partner status and country. Bonferroni adjustment for multiple comparisons.

depressive symptomatology, less anxiety and better mood state. Across patient groups, positive mood and lower depression and anxiety levels were thus strongly associated with better social functioning, even more so than severity of disease per patient group.

## DISCUSSION

The current study presents novel findings from the pan-European PRISM project on cross-disorder and disorder-specific deficits in social functioning among SZ and AD patients. As compared to HC, both behavioral and affective social functioning are clearly poorer in SZ patients (Cohen's  $d$ 's 0.81-1.69), whereas AD patients have mostly poorer behavioral social function (Cohen's  $d$ 's 0.65-1.14). Behavioral indices of social functioning were fairly similar across patient groups, SZ patients have more feelings socially disability than AD patients (Cohen's  $d$  0.65). Across patient groups, positive mood, lower depression and anxiety levels were strong determinants of better social functioning ( $p$ 's <0.001), even more so than severity of disease. Overall, this indicates that SZ and AD patients have rather similar social functioning levels in terms of behavior, but affective social functioning is different.

Consistent with our earlier observations<sup>35</sup>, we observed a putative lack of insight among AD patients, who perceive their social disability on the same level as healthy controls, whereas AD informants and research staff perceive their social disability as significantly more impaired. By contrast the current data suggest that SZ patients are more aware of their own social disabilities than AD patients, an observation that warrants further investigation in future studies.<sup>40</sup> Findings are in line with previous research in AD patients where it was shown that a strong self-concept was associated with larger social dysfunction discrepancy comparing self-rating with caregiver rating.<sup>18</sup> Interestingly, social functioning in both diagnostic groups was found to be more strongly associated with mood than by current state of the disorders.

For SZ patients impairments in behavioral social functioning are consistently described<sup>8,41,42</sup>, as are impairments in affective social functioning, such as feeling lonely and socially impaired.<sup>43-45</sup> Our results seem consistent with and replicate this previous SZ research. Findings for AD patients are less unequivocal. Impairments in behavioral social functioning for AD patients are described as rather subtle in an early stage of the disease.<sup>15,27</sup> In our study, however, AD patients differed from their matched HC group on most behavioral social functioning indices. It is possible that broad assessment of social functioning as implemented here could easier

Table 5: Adjusted† associations of clinical characteristics and various social functioning indicators within the group of patients (AD N=50, SZ=56)

|                                     | ADAS-Cog |   | PANSS positive symptoms |   | PANSS negative symptoms | Depression severity | Anxiety severity | PANAS positive affect | PANAS negative affect |
|-------------------------------------|----------|---|-------------------------|---|-------------------------|---------------------|------------------|-----------------------|-----------------------|
|                                     | AD only  | β | SZ only                 | β | SZ only                 | AD and SZ           | AD and SZ        | AD and SZ             | AD and SZ             |
| <b>Behavioral social indicators</b> |          |   |                         |   |                         |                     |                  |                       |                       |
| Social withdrawal                   | 0.173    |   | -0.224                  |   | -0.053                  | -0.555***           | -0.413***        | 0.414***              | -0.355**              |
| Interpersonal functioning           | -0.059   |   | -0.072                  |   | -0.330*                 | -0.522***           | -0.424***        | 0.468***              | -0.309**              |
| Independence-competence             | -0.166   |   | 0.009                   |   | -0.224                  | -0.151              | -0.132           | 0.158                 | -0.175                |
| Independence-performance            | -0.158   |   | -0.039                  |   | -0.151                  | -0.102              | -0.121           | 0.166                 | -0.091                |
| Recreational activities             | -0.263   |   | -0.124                  |   | -0.021                  | -0.166              | -0.169           | 0.395***              | -0.158                |
| Pro-social activities               | -0.400*  |   | -0.054                  |   | -0.077                  | -0.312**            | -0.165           | 0.366***              | -0.043                |
| Total SFS score                     | -0.242   |   | -0.111                  |   | -0.205                  | -0.498***           | -0.399***        | 0.561***              | -0.310**              |
| <b>Affective social indicators</b>  |          |   |                         |   |                         |                     |                  |                       |                       |
| Perceived social disability         | 0.194    |   | -0.082                  |   | 0.238                   | 0.650***            | 0.423***         | -0.516***             | 0.274**               |
| Rater-perceived social disability   | 0.322    |   | -0.274                  |   | 0.177                   | 0.424***            | 0.232*           | -0.336**              | 0.125                 |
| Loneliness                          | -0.163   |   | 0.278*                  |   | 0.227                   | 0.653***            | 0.495***         | -0.370**              | 0.445***              |

† adjusted for sex, age, educational years, partner status and country

\*p-value < 0.05, \*\* p-value < 0.01, \*\*\* p-value < 0.001

reveal subtle differences in specific aspects of social behavior. Among affective social indicators, feelings of loneliness were similar between AD and their matched healthy controls, as was found before.<sup>46</sup>

When comparing SZ and AD patients on behavioral social functioning, a highly similar pattern of (dys)functioning emerged. This was especially true for the combined SFS outcomes. The largest differences between the patient groups emerged for the affective social indicators. For instance, patients with SZ evaluated themselves as less capable in social contact than AD patients. This suggests that patients have quite similar social functioning behavior but may evaluate this differently. It has been shown that feelings of loneliness are not necessarily reflected by objective social isolation.<sup>43,47</sup> AD patients evaluated their perceived social disability on the same level as their matched healthy controls, whereas an informant evaluated their social abilities as strongly impaired. This suggests that AD patients may have an overly positive view of their own social functioning, possibly leading to underreporting of their impairments. This overestimation of their own social functioning, as compared to informants, has been described before<sup>18,35</sup> and has been linked to loss of awareness due to AD.<sup>17</sup> Lack of awareness of social dysfunction is related to greater distress among the caregivers of AD patients.<sup>17,48</sup> Mood influenced social functioning to a large extent, especially the affective indicators, with better mood associated with more favorable affective social outcomes. The large impact of anxiety and depressive disorders on social functioning has been described before, although the underlying pathophysiological mechanisms remain largely unknown. One hypothesis argues that imbalanced brain network function (especially in the brain's default mode network<sup>49</sup>) not only impedes adaptive social functioning, but also interferes with maintenance of stable (positive) mood<sup>28,50,51</sup>. Current severity of disease in SZ and AD had only minor influence on social functioning indicators, as was previously found for AD<sup>16</sup> and SZ<sup>41</sup>, although the reverse has been described as well.<sup>42,46</sup>

The PRISM study described here is unique in its comparison of two patient groups with distinctive pathologies and age-ranges, in relation to various indicators of social functioning. However, some limitations inherent to the study should be mentioned. First, our data are cross-sectional, thereby not allowing for causal interpretations. Second, data is based on self-evaluation (with exception of the rater-perceived social disability score), which may have resulted in biased responding. Passive monitoring of social behavior is a promising development to objectively measure ambulatory behavior and tackle possible self-report bias. Smartphone technology such as the BEHAPP-app<sup>35,52,53</sup> will allow the comparison of perceived social functioning with objective measurements. Third, we excluded

the employment subscale of the SFS since we believe it would introduce a bias between SZ and AD patients, since most AD patients and older HC's were retired or not working, in line with other research.<sup>30</sup> However, inclusion of the employment subscale would arguably increase differences in social functioning between the SZ and younger HC's. Fourth, we made a distinction between behavioral (i.e. more quantitative) and affective (i.e. more perceptions of own social dysfunction) social indicators, which bears some clear benefits and is supported by prior work, but may ultimately pose an oversimplification of a complex phenomenon. Future work is therefore warranted to further explore and validate the findings and interpretations of the current study.

In summary, the present study reveals that behavioral aspects of social functioning are rather similarly affected in SZ and AD, whilst the affective perception of this behavior seems partly different in the two patient groups. Patients diagnosed with AD evaluate their interpersonal relations as only mildly impaired, whereas patients diagnosed with SZ have a more negative perspective of their own social functioning. AD patients may underreport their impairments in social functioning. Future research on social functioning should make a distinction between behavioral and affective indicators of social functioning, as these may associate differentially with pathophysiology. Findings further suggest that mood is highly associated with social functioning. This study may serve as a point of departure for future cross-disorder studies into the neurobiological underpinnings of social impairments in SZ and AD.

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Supplement 1

Table S1.1. Factor analyses of the six subscales of the Social Functioning Scale

|                          | Factor loading<br>(N=164) |
|--------------------------|---------------------------|
| Withdrawal               | .685                      |
| Interpersonal            | .714                      |
| Independence-competence  | .653                      |
| Independence-performance | .736                      |
| Recreation               | .745                      |
| Prosocial                | .787                      |
| Eigenvalue               | 3.121                     |
| % Variance explained     | 52.02                     |

Supplement 2

Table S2.1. Mean scaled social functioning scale scores (N=163)

|                                      | Schizophrenia<br>patients<br>N = 56 | Younger<br>healthy<br>controls<br>N = 29 | Alzheimer's<br>disease<br>patients<br>N=50 | Older<br>healthy<br>controls<br>N= 28 |
|--------------------------------------|-------------------------------------|------------------------------------------|--------------------------------------------|---------------------------------------|
| Social withdrawal, mean (SD)         | 102.7 (11.2)                        | 120.5 (10.9)                             | 114.4 (10.4)                               | 120.8 (10.6)                          |
| Interpersonal functioning, mean (SD) | 112.8 (19.0)                        | 140.0 (10.5)                             | 130.1 (17.1)                               | 140.8 (9.5)                           |
| Independence-competence, mean (SD)   | 110.9 (9.8)                         | 120.0 (5.6)                              | 106.4 (8.4)                                | 117.1 (6.7)                           |
| Independence-performance, mean (SD)  | 108.3 (10.0)                        | 118.3 (7.6)                              | 107.0 (8.4)                                | 115.5 (6.0)                           |
| Recreation activities, mean (SD)     | 107.0 (8.4)                         | 120.2 (13.5)                             | 120.4 (14.8)                               | 132.4 (10.5)                          |
| Prosocial activities, mean (SD)      | 118.6 (12.4)                        | 131.8 (6.4)                              | 124.5 (9.2)                                | 130.9 (8.9)                           |
| Total SFS score, mean (SD)           | 111.2 (1.7)                         | 125.3 (2.1)                              | 116.5 (1.9)                                | 124.9 (2.0)                           |

Supplement 3

Table S3.1. Perceived social disability (WHO-DAS score) availability across patient groups

|                                   | Schizophrenia patients<br>(N=56) | Alzheimer's disease patients<br>(N=50) |
|-----------------------------------|----------------------------------|----------------------------------------|
| Patient rated score, mean (SD)    | 11.1 (5.1) 0 missing             | 6.4 (2.1) 0 missing                    |
| Caregiver rated score, mean (SD)  | 12.4 (4.5) 31 missing            | 9.8 (3.4) 12 missing                   |
| Researcher rated score, mean (SD) | 12.7 (4.8) 7 missing             | 10.8 (3.8) 11 missing                  |

Table S3.2. Perceived social disability correlations across groups

|                  | Participant rated<br>Total (n=163) | Caregiver rated<br>Total | Participant rated<br>SZ (N=56) | Caregiver rated<br>SZ | Participant rated<br>AD (N=50) | Caregiver rated<br>AD | Participant rated<br>HC (N=57) |
|------------------|------------------------------------|--------------------------|--------------------------------|-----------------------|--------------------------------|-----------------------|--------------------------------|
| Caregiver rated  | .47**                              | 1                        | .60**                          | 1                     | .29*                           | 1                     | NA                             |
| Researcher rated | .71**                              | .80**                    | .83**                          | .79**                 | .25                            | .79**                 | .84**                          |

\*p-value < 0.05 \*\* p-value<0.001

Abbreviations: SZ, schizophrenia, AD: Alzheimer’s disease, HC: healthy controls.

## Chapter 4

# Default Mode Network Connectivity and Social Dysfunction in Major Depressive Disorder

4

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## ABSTRACT

**BACKGROUND:** Though social functioning is often hampered in Major Depressive Disorder (MDD), we lack a complete and integrated understanding of the underlying neurobiology. Connectional disturbances in the brain's Default Mode Network (DMN) might be an associated factor, as they could relate to suboptimal social processing. DMN connectional integrity, however, has not been explicitly studied in relation to social dysfunctioning in MDD patients.

**METHODS:** Applying Independent Component Analysis and Dual Regression on resting-state fMRI data, we explored DMN intrinsic functional connectivity in relation to social dysfunctioning (i.e. composite of loneliness, social disability, small social network) among 74 MDD patients (66.2% female, Mean age=36.9,  $SD=11.9$ ). Categorical analyses examined whether DMN connectivity differs between high and low social dysfunctioning MDD groups, dimensional analyses studied linear associations between social dysfunction and DMN connectivity across MDD patients. Threshold-free cluster enhancement (TFCE) with family-wise error (FWE) correction was used for statistical thresholding and multiple comparisons correction ( $P<0.05$ ).

**RESULTS:** The analyses cautiously linked greater social dysfunctioning among MDD patients to diminished DMN connectivity, specifically within the rostromedial prefrontal cortex and posterior superior frontal gyrus.

**CONCLUSIONS:** These preliminary findings pinpoint DMN connectional alterations as potentially germane to social dysfunction in MDD, and may as such improve our understanding of the underlying neurobiology.

## INTRODUCTION

Adaptive social functioning is necessary for human survival.<sup>1,2</sup> Regretfully, social behavior is often severely hampered in neuropsychiatric diseases such as Major Depressive Disorder (MDD)<sup>3,4</sup> with residual dysfunction remaining even after complete remission of depressive symptoms.<sup>5,6</sup> Recent data even suggests that successful MDD remission requires not only a decrease in depressive symptoms but also significant improvements in the social domain.<sup>4</sup> Consonant with this premise, dysfunctions in the social domain are considered an important aspect of MDD<sup>7</sup> and are according to patients one of the most debilitating consequences of the disorder.<sup>8</sup> Social dysfunction has been studied and established in various ways in MDD patients over the years<sup>7,9</sup>, yet a complete and integrated understanding of the underlying neurobiology is still lacking.<sup>3,4</sup> Knowledge on how major neurobiological systems may contribute to social dysfunction in MDD could allow novel insights into underlying pathomechanisms and aid clinical care.

A neurobiological system potentially relevant to both social (dys)functioning and MDD pathophysiology is the brain's Default Mode Network (DMN), which has been shown to play a critical role in various aspects of human social behavior.<sup>10–14</sup> The complexity of DMN function and its subsystems is reflected by the broad scope of brain areas involved in the DMN.<sup>14–16</sup> The DMN consists of 2 subsystems and one mediating core system.<sup>15</sup> The core DMN system mainly processes personally relevant, sociocognitive information, with the rostromedial prefrontal cortex (PFC) and posterior cingulate cortex being its key nodes.<sup>14,15</sup> The medial temporal DMN subsystem is associated with recollection of experiences and autobiographical processing, and is comprised of the hippocampal formation, retrosplenial cortex, inferior parietal lobule, and ventromedial PFC.<sup>14,15</sup> The dorsal medial DMN subsystem, on the other hand, is predominantly involved in socially-colored, meta-cognitive processes and mentalizing (i.e., inferences about others' internal state).<sup>14,15</sup> The dorsal medial subsystem comprises the temporal poles, lateral temporal cortex, temporoparietal junction, superior frontal gyrus and dorsomedial PFC.<sup>14,15</sup> The different subsystems of the DMN are highly intertwined and this allows for complex interactions and parallel functioning, which is a key ingredient to DMN modulation of intricate human social behaviors.<sup>15</sup> Along the same line, disturbances in one area or subsystem of DMN tend to trigger widespread disruptions across the DMN.<sup>14,15</sup> A whole-network approach of DMN among socially dysfunctional MDD patients, capturing DMN network connectivity in its entirety, thus seems more adequate as an initial, hypothesis-generating step than investigating DMN subsystems.

Alterations in DMN connectional integrity among MDD patients have been described in several overview papers, and putatively linked to deficits in sociocognitive processes that the DMN seems to subserve (e.g., self-referential processing, mentalizing, emotion recognition/resonance).<sup>4,17–19</sup> The most consistent finding across all studies is altered functional connectivity patterns within prefrontal nodes of the DMN, particularly in rostromedial/ventromedial PFC regions.<sup>17,19–23</sup> Of note, DMN disturbances are also observed in other neuropsychiatric disorders characterized by severe social dysfunctioning, including autism, schizophrenia and social phobia,<sup>24–26</sup> thus further corroborating the importance of DMN to both normal and disturbed social functioning. As stated by Kaiser et al.<sup>18</sup> in their seminal overview paper, specific patterns of network dysfunction may contribute to core deficits in social, cognitive, and affective functions that could trigger clinical symptoms in neuropsychiatric disorders such as MDD. Hence, a functional network approach towards social functioning in MDD offers the opportunity to study the dynamics of interconnected areas that interact to allow adaptive social behavior.

In summary, social function is often severely impaired in MDD, and alterations in key social processes may be reflected by changes in DMN connectivity. To our knowledge, the intrinsic connectional integrity of DMN has not been studied yet in relation to social dysfunction in MDD. Probing how social dysfunction may both categorically and dimensionally<sup>27–29</sup> relate to DMN connectivity in MDD could, however, further our understanding of underlying neurobiology and plausibly aid future treatment strategies. This premise is increasingly echoed in the field, and in particular by the Pan-European PRISM study<sup>30</sup>, which upholds that social dysfunction may have a distinct neurobiological signature, be transdiagnostic in nature, and carry clinical/therapeutic relevance. Social functioning, however, is a complex and dynamic process, and often difficult to capture adequately along one specific domain. In order to cover social functioning more broadly and fully, here we assess the cumulative association of three important social dysfunction indices and DMN connectivity within MDD patients. These indices include loneliness, perceived social disability, and small social network; factors not only present among MDD patients in varying levels but also associated with adverse neurobiological changes.<sup>11,31–38</sup> Using this cumulative social dysfunction score, we explored the effect of social dysfunction on DMN whole-network connectivity among MDD patients, both categorically and dimensionally. The categorical analyses examined whether DMN connectivity differs between high and low social dysfunction MDD groups, while the dimensional analysis tested whether a linear association can be found between social dysfunction and DMN connectivity across MDD patients.

Post-hoc sensitivity analyses additionally investigated the influence of current comorbid anxiety disorder, antidepressant use, and depression severity on DMN-social dysfunction relationships.

## MATERIALS AND METHODS

### Participants

Participants were recruited from the longitudinal, naturalistic Netherlands Study of Depression and Anxiety (NESDA<sup>57</sup>). The study protocol for NESDA was carried out in accordance with guidelines approved by the Ethical Review Board of the VU University Medical Centre and by local review boards at each participating centre (University Medical Center Groningen (UMCG), Leiden University Medical Center (LUMC)). Informed written consent was given by all participants. DSM-IV diagnoses of current (6-month recency) MDD were established using the Composite International Diagnostic Interview lifetime version 2.1. Exclusion criteria for MDD patients within the NESDA-MRI study were the presence of Axis I disorders other than depressive or anxiety disorders (i.e., panic, social anxiety and/or generalized anxiety disorder), use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors or infrequent benzodiazepine use, presence or history of major internal or neurological disorder, dependency or recent abuse (past year) of alcohol or drugs, hypertension, presence of MRI-contraindications and not being fluent in Dutch language. MDD patients were recruited through general practitioners, primary care, and specialized mental care institutions. Resting-state fMRI data were available for 120 participants with depression. Participants were excluded if their fMRI images were of substandard quality (e.g., due to movements or technical issues,  $N=24$ ) or data were missing on social dysfunctioning questionnaires ( $N=22$ ). We included 74 individuals with a 6-month DSM-IV diagnosis of MDD (mean age = 36.9,  $SD = 11.9$ ; 66.2% female).

### Social Dysfunction

To cover social dysfunctioning a social composite score was calculated using three validated (subscales of) questionnaires that probed loneliness, perceived social disability, and small social network size. These three proxy indicators are moderately correlated with each other ( $r = 0.40$ – $0.50$ ,  $P$ 's  $< 0.01$ ) and have been shown predictive of social dysfunctioning and adverse neurobiological changes.<sup>11,32–37,41–43</sup> These three indicators of social dysfunctioning moreover emerged as being prominently affected in MDD patients as compared to healthy controls in a separate study by our group (effect sizes ranging from 0.54 to 1.19<sup>38</sup>), and also are employed in the Pan-European PRISM study on the neurobiology of social dysfunction.<sup>30</sup> Subjective

feelings of loneliness were measured using the loneliness questionnaire<sup>58</sup>, which consists of 11 items that are scored on a 3-point Likert scale. Perceived social disability, or difficulties in making new or maintaining friendships, was measured using the social interaction subscale domain of the World Health Organization Disability Assessment Schedule (WHO-DAS)<sup>59,60</sup>, which consists of 5 items that are scored on 5-point Likert scale. Social network size was assessed using the close person inventory<sup>61,62</sup>, wherein the number of adults with whom the participant has regular and important contact with is scored on a 6-point ordinal scale (number of individuals in a network: >20, 16-20, 11-15, 6-10, 2-5, 0-1). The social network size scores were reversed, so that in line with the other two questionnaires higher scores would denote more social dysfunction, hence allowing for a more intuitive and reliable composite score. In line with prior work<sup>63</sup>, this composite score was calculated by first log transforming and standardizing the individual questionnaire scores, subsequently summing them up, and then dividing the sum by three. A higher composite score thus indicates more social dysfunction (more loneliness, higher perceived social disability, smaller social network). The correlations between this composite score and the individual questionnaires were all above  $r = 0.73$  ( $P$ 's < 0.001). This social dysfunction composite score thus captures multiple domains of social dysfunctioning at once and more fully, makes multiple testing of each individual measure redundant, and allows insight into the cumulative effect of social dysfunction on brain network connectivity.

### MRI Data Acquisition

Imaging data were acquired using Philips 3T MR- systems (Best, the Netherlands) located at the LUMC, AMC, and UMCG, equipped with a SENSE-8 (LUMC and UMCG) and a SENSE-6 (AMC) channel head coil respectively. Resting-state fMRI (RS-fMRI) data were acquired using a T2-weighted gradient echo echo-planar imaging with the following scan parameters in Amsterdam and Leiden: 200 whole-brain volumes; repetition time (TR) 2300 ms; echo time 30 ms; flip angle 80°; 35 transverse slices; no slice gap; field of view 220x220 mm; in-plane voxel size 2.3x2.3 mm; slice thickness 3 mm; duration 7.51 min. Parameters in Groningen were identical, apart from: echo time 28 ms; 39 transverse slices; in-plane voxel size 3.45x3.45 mm. A sagittal 3-dimensional gradient-echo T1-weighted image was acquired for registration purposes and gray matter analysis with the following scan parameters: repetition time 9 ms; echo time 3.5 ms; flip angle 80°; 170 sagittal slices; no slice gap; field of view 256x256 mm; 1 mm isotropic voxels; duration 4.5 min. In the darkened MRI room participants were instructed to lie still with their eyes closed and not to fall asleep. Participants confirmed wakefulness after the scanning session. No abnormalities were found upon inspection of the subjects' structural images by a neuroradiologist.

### MRI Data Preprocessing

The RS-fMRI imaging data was preprocessed and analyzed using sing FMRIB Software Library (FSL) version 5.0.10 and included removing of scanner, (micro) motion, and physiological artefacts using a combination of FSL FIX<sup>64</sup>, ICA-AROMA<sup>65</sup>, motion correction (realignment) using McFLIRT<sup>66</sup>, grand mean scaling, spatial smoothing with 6mm Gaussian kernel, high pass filtering (Gaussian-weighted least-squares straight line fitting with a .01 Hz cut-off ) and is described in depth elsewhere.<sup>67</sup> Additional nuisance signal regression was performed according to pipeline recommended in (50) and consisted of regressing mean signals from the cerebrospinal fluid (CSF) and white matter (WM). CSF and WM masks were obtained by multiplying subject-specific T1 segmentations obtained using FSL's FAST<sup>68</sup> with the MNI152-based CSF and WM anatomical priors provided as part of FSL and thresholded with a 0.95 threshold. The resulting RS-fMRI images were registered to Montreal Neurological Institute (MNI) space using transformation matrices obtained from the first co-registration of functional images to T1 image using the FLIRT boundary based registration tool<sup>69</sup> and registering the T1 images to MNI template brain using FMRIB's linear image registration tool (FLIRT).<sup>70</sup> Participants were excluded if head movement was above 2.5 mm | 0.4 rad, or if functional images were of insufficient quality.

### Functional Connectivity Analysis

Figure 1 depicts the analytical pipeline employed in this study, which we will further outline in the following paragraphs. Functional connectivity analysis was carried out using probabilistic Independent Component Analysis (ICA;<sup>71</sup>), as implemented in FSL's Multivariate Exploratory Linear Decomposition into Independent Components tool (MELODIC). Default group ICA processing steps were applied to the individual preprocessed and normalized data sets: masking of non-brain voxels, voxel-wise de-meaning of the data, and normalization of the voxel-wise variance based on all data sets. Subsequently, the preprocessed data were concatenated in time to create a single 4D data set that was then projected into a 20-dimensional subspace using principal component analysis. The observations were decomposed into 20 sets of independent vectors that describe signal variation across the temporal (time courses) and spatial (maps) domains by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique. We chose to use 20 independent components to reach the same balance between the amount of clustering and splitting as previous studies applying the same techniques and capture the complete DMN.<sup>40,56</sup> In short, probabilistic ICA within MELODIC thus uses all the data available within the fMRI dataset to decompose the entire temporal fMRI dataset into independent spatial components, which relate to intrinsically connected functional brain networks. The set of spatial maps/components generated by MELODIC was

used to generate subject-specific versions of the spatial maps, and associated time courses, using Dual Regression.<sup>72</sup> That is, for each subject, the group-average set of spatial maps was regressed (as spatial regressors in multiple regression) onto the subject's 4D space-time dataset. This resulted in a set of subject-specific time series, one per group-level spatial map. Next, these time series were regressed (as temporal regressors, again using multiple regression) against the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

Our component of interest (i.e., DMN; Figure 1) was then selected based on spatial similarity to functional networks described in prior seminal papers on DMN large-scale connectivity and architecture (e.g.,<sup>40,72</sup>). This component, reflecting the DMN, included the vmPFC, posterior cingulate, retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, and dmPFC. The composite social dysfunction score was used in subsequent statistical inferences to assess the relation between social dysfunction and DMN connectivity in MDD patients, both categorically and dimensionally. In the categorical analyses, MDD patients were divided into a high and a low social dysfunction group based on the group median of the social dysfunction composite (Median = 0.44), and the analyses examined whether the association between composite and DMN connectivity differed between the two groups. The dimensional analysis included all MDD patients in one large group and assessed whether across participants a linear association could be found between individual participant's composite score and DMN connectivity.

All statistical analyses were performed using FSL's non-parametric, permutation-based Randomise tool<sup>73</sup>, which included 5000 random permutations to build up the null distribution of the cluster size statistic while testing our contrasts of interest in the categorical and dimensional analyses. Four nuisance regressors (all demeaned across participants) describing age, sex, education, and scanner location were added to the model. Statistical maps were thresholded using Threshold-Free Cluster Enhancement (TFCE,<sup>74</sup>) with family-wise error (FWE) correction at  $P < 0.05$  to control for multiple comparisons. TFCE is currently one of the most robust methods for finding significant "clusters" in voxelwise MRI data, without having to define clusters in a binary.<sup>74,75</sup> Cluster-like structures are enhanced but the image remains fundamentally voxelwise.<sup>74</sup> The control of multiple comparisons across relevant voxels was achieved through sequential/serial FWE-correction<sup>74</sup> with  $\alpha = 0.05$ , meaning the chance of false positives occurring over the entire voxel space is no more than 5%.

## Sensitivity Analyses

Similar to prior work<sup>76,77</sup>, we performed post-hoc sensitivity analyses to examine the association between current comorbid anxiety disorders and antidepressant use and DMN connectivity. Using individual participants' connectivity strength level (i.e., mean Z-scores) within DMN regions of significant effect, analyses of variance (ANOVA's) were conducted to compare MDD patients with high versus low social dysfunction, excluding either those with a comorbid disorder or those using antidepressants. Finally, we explored whether covarying for comorbidity and antidepressant use, on top of age, sex, education, and scanner location, would affect any of the findings. All analyses were done using SPSS version 22.0 (SPSS Inc, Chicago, Illinois).

## RESULTS

### Sample Characteristics

The mean age of the study sample ( $N=74$ ) was 36.9 years ( $SD=11.9$ ) and 66.2% were females (Table 1). MDD patients low in social dysfunction were younger, more often female and had a higher level of education. Whereas depressive symptom severity was slightly higher in the MDD high social dysfunction group, the other clinical psychiatric characteristics (comorbid anxiety disorder, antidepressant use, symptom duration, age of onset) did not differ between groups. Within the total sample, 54.1% had a current comorbid anxiety disorder and a mean IDS score of 21.5 (mild depressive symptomatology). Participants had symptom durations of on average 33.5% of all follow-up months and the mean age of onset was 25.1 years. Antidepressants were used by 31.1% of the participants.

### Functional Connectivity Analysis

Twenty functional networks were generated during the probabilistic Independent Component Analysis (ICA) and entered into Dual Regression, with the DMN network being selected for further analysis (Figure 1 & 2). The DMN has been consistently found across subjects and over time using the same methods as applied here<sup>39,40</sup>, with DMN architecture also emerging among all of our participants. Using the composite social dysfunction score, we next examined the association of social dysfunction and DMN connectivity in MDD patients, both categorically and dimensionally. Whole-DMN *categorical* analyses revealed diminished DMN connectivity in high social dysfunction MDD patients, specifically within the rostromedial prefrontal cortex (rmPFC) and posterior superior frontal gyrus (psFG) subsections of the DMN (TFCE & FWE corrected,  $P < 0.05$ ) (Figure 2). Our whole-DMN dimensional analyses similarly suggested a pattern of reduced DMN connectivity as a function of more

Table 1: Sample Characteristics

| Variable                                 | MDD high social<br>dysfunction<br>(N=37) | MDD low social<br>dysfunction<br>(N= 37) | p-value, effect<br>sizes<br>(Cohen's d Phi) | MDD entire<br>sample<br>(N=74) |
|------------------------------------------|------------------------------------------|------------------------------------------|---------------------------------------------|--------------------------------|
| Age (mean ± SD)                          | 39.8 (11.9)                              | 33.9 (11.3)                              | 0.03; 0.5                                   | 36,9 (11,9)                    |
| Sex (% female)                           | 51.4%                                    | 81.1%                                    | 0.01; 0.3                                   | 66,2%                          |
| Years of education (mean ± SD)           | 11.4 (2.0)                               | 12.6 (2.9)                               | 0.03; 0.5                                   | 12,0 (2,4)                     |
| Number of individuals per scan site      |                                          |                                          |                                             |                                |
| UMCG Groningen                           | 15                                       | 8                                        |                                             |                                |
| LUMC Leiden                              | 15                                       | 18                                       |                                             |                                |
| Amsterdam UMC, Amsterdam                 | 7                                        | 11                                       |                                             |                                |
| Comorbid anxiety disorder (%)            | 64.7%                                    | 43.2%                                    | 0.06; -0.2                                  | 54.1%                          |
| Antidepressant use (%)                   | 40.5%                                    | 21.6%                                    | 0.08; -0.2                                  | 31.1%                          |
| Depression severity (IDS) (mean ± SD)    | 26.6 (11.1)                              | 19.7 (10.2)                              | 0.01; 0.6                                   | 23.1 (11.2)                    |
| Symptom duration (% time with symptoms)  | 39.7%                                    | 27.2%                                    | 0.06; 0.5                                   | 33.5%                          |
| Age of onset (years) (mean ± SD)         | 25.6 (11.9)                              | 24.7 (10.7)                              | 0.01; 0.01                                  | 25.1 (11.3)                    |
| Social Dysfunction                       |                                          |                                          |                                             |                                |
| Standardized/log-transformed (mean ± SD) |                                          |                                          |                                             |                                |
| - Social dysfunction composite **        | 0.9 (0.2)                                | -0.02 (0.5)                              | 0,00; 2,9                                   | 0.4 (0.6)                      |
| Loneliness**                             | 1.0 (0.3)                                | 0.1 (0.7)                                | 0,00; 1,7                                   | 0.6 (0.7)                      |
| Perceived social disability**            | 1.1 (0.3)                                | 0.0 (0.8)                                | 0,00; 1,8                                   | 0.6 (0.8)                      |
| Small Social Network**                   | 0.6 (0.3)                                | -0.2 (1.0)                               | 0,00; 1,1                                   | 0.2 (0.9)                      |
| Raw (mean ± SD)                          |                                          |                                          |                                             |                                |
| Loneliness**                             | 8.7 (2.4)                                | 4.2 (2.6)                                | 0,00; 1,8                                   | 6,4 (3,4)                      |
| Perceived social disability**            | 15.7 (3.4)                               | 9.8 (3.7)                                | 0,00; 1,7                                   | 12,8 (4,5)                     |
| Small Social Network**                   | 5.1 (0.5)                                | 3.9 (1.0)                                | 0,00; 1.5                                   | 4.5 (1.0)                      |

Chi-square tests were employed for categorical variables, and independent sample t-test for continuous variables. Effect sizes for continuous data was calculated using Cohen's *d*, for dichotomous data phi coefficient. Higher scores on social dysfunction measures denote more subjectively experienced social dysfunction. A higher social dysfunction composite score thus indicates more severe social dysfunction (more loneliness, higher perceived social disability, smaller social network). IDS = Inventory of depressive symptomatology. \* =  $P < 0.05$ ; \*\*  $P < 0.001$ ; ns = not significant at  $P < 0.05$   
Note: Data on depressive duration missing in 1 MDD patient with low social dysfunction.

Data on depressive severity missing in 2 MDD patients: 1 high and 1 low on social dysfunction.

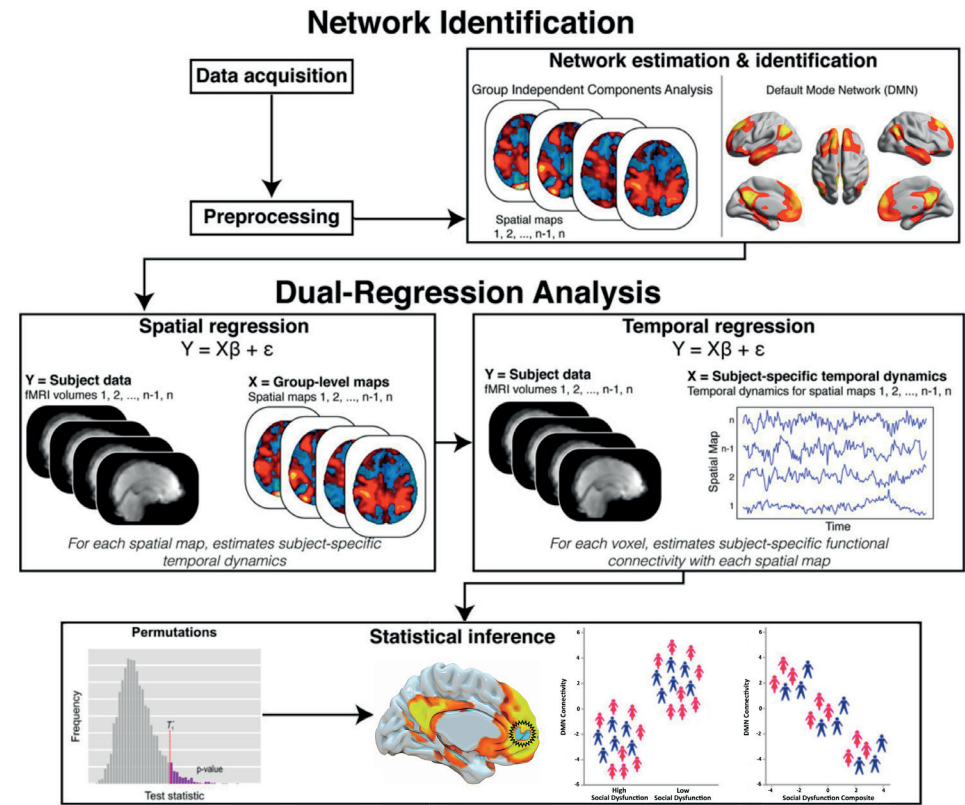
social dysfunction, though this effect was not statistically significant (*TFCE* & *FWE* corrected,  $P = 0.33$ ). Exploratory analyses revealed that at a more lenient threshold ( $P < 0.001$ , uncorrected), the same pattern of diminished DMN connectivity within the left rmPFC and pSFG could be observed, with an average correlation  $r = -0.43$ ,  $P$ -uncorrected  $< 0.001$ . When we moreover reran the *dimensional analyses* focusing specifically on effect sites from the *categorical analysis* (i.e., parts of the left rmPFC and pSFG), we similarly found an association between diminished DMN connectivity and higher social dysfunction levels across participants (*TFCE* & *FWE* corrected,  $P < 0.05$ ) with an average correlation  $r = -0.58$ ,  $P$ -corrected  $< 0.05$  (see figure 2). Taken as a whole, our analyses cautiously link more severe social dysfunctioning among MDD patients to diminished DMN connectivity, in particular when comparing low and high social dysfunctioning MDD patients.

Sensitivity Analyses

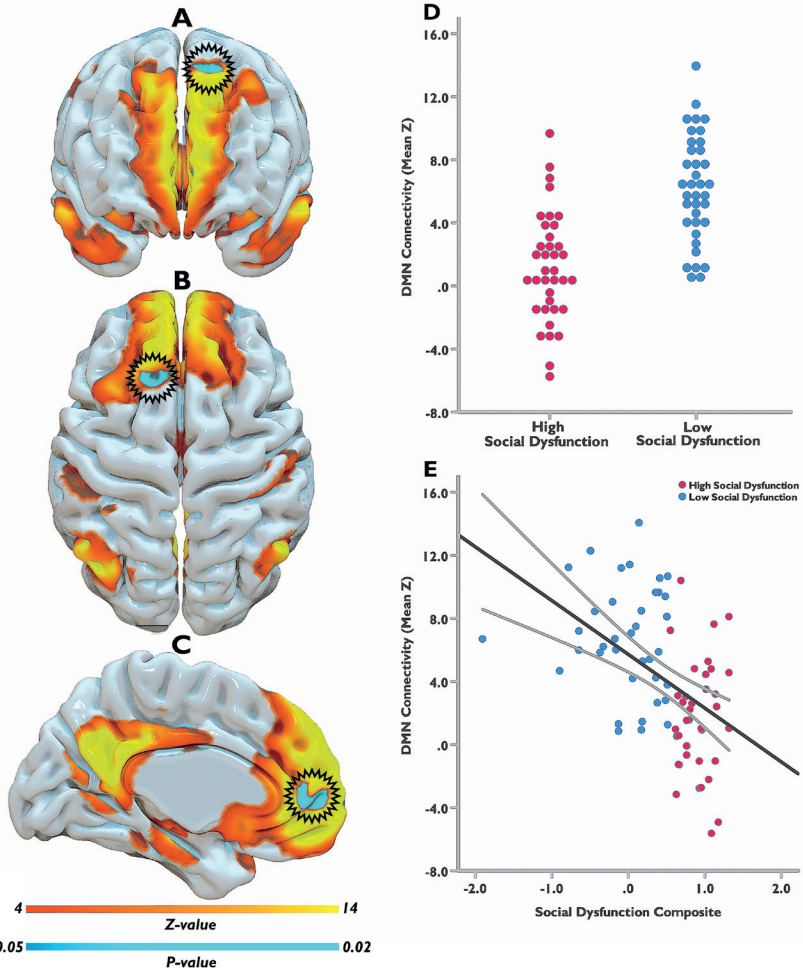
The post-hoc sensitivity analyses revealed that between-group differences in DMN connectivity in high vs. low social dysfunctioning MDD groups remained significant, while excluding MDD patients with current comorbid anxiety disorders ( $N = 40$  excluded) ( $F(1,27) = 21.98$ ,  $P < 0.05$ ) or using antidepressants ( $N = 23$  excluded) ( $F(1,44) = 66.84$ ,  $P < 0.05$ ). Including all patients and covarying for comorbidity, antidepressant use, and depression severity, on top of age, sex, education, and scanner location, also did not affect the documented between-group DMN effects ( $F(1,64) = 48.26$ ,  $P < 0.05$ ).

Composite Score vs. Individual Social Dysfunction Indices

We opted to use a cumulative measure of social dysfunctioning and examine its association with DMN connectivity among MDD patients. This cumulative measure was generated by combining three separate questionnaires that were most affected in MDD patients with social dysfunction, as reflected in their medium to large effect sizes (ranging from 0.54-1.19). In addition, for these three questionnaires, there is considerable evidence of their impact on neurobiological indicators.<sup>11,32-37,41-43</sup> Lastly, these indicators are also employed in the Pan-European PRISM study on the neurobiology of social dysfunction.<sup>30</sup> Each questionnaire assesses a different domain of social dysfunction: loneliness, perceived social disability, and a small social network. This resulted in a social dysfunction composite index that a) captures multiple domains of social dysfunctioning at once and more fully than each individual measure separately, 2) makes multiple testing of brain-behavior relations for each individual measure redundant, 3) and allows insight into the *cumulative association* of social dysfunction on brain network connectivity. The fact that the three separate questionnaires were also highly correlated ( $r = 0.40-0.50$ ,  $P$ 's  $< 0.01$ ), and thus prone to multicollinearity, further justifies the use of the composite score



**Figure 1. Functional connectivity analyses of the Default Mode Network (DMN).** Collected resting-state fMRI data were first extensively preprocessed and cleaned<sup>67</sup>. Data from all participants was next concatenated across time and submitted to a probabilistic group independent component analysis (ICA) using MELODIC. The group ICA produced a set of 20 independent spatial maps/components (i.e., functional networks). The set of spatial maps generated by MELODIC was then used to generate subject-specific versions of these spatial maps, and associated time courses, using Dual Regression. That is, for each subject, the group-average set of spatial maps was regressed (as spatial regressors in multiple regression) onto the subject's 4D space-time dataset. This resulted in a set of subject-specific time series, one per group-level spatial map. Next, these time series were regressed (as temporal regressors, again using multiple regression) against the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. Our component of interest (i.e., DMN) was then selected based on spatial similarity to functional networks described in prior seminal papers on DMN connectivity and architecture. Finally, permutation testing ( $N=5000$ ) was used to probe the association between DMN connectivity and social dysfunction, both categorically and dimensionally, while correcting for age, sex, education, and scanner location. Results were adjusted for multiple comparisons using Threshold-Free Cluster Enhancement with Family-Wise Error correction at  $P<0.05$ . Adapted and reprinted with permission from Wiley Periodicals, Inc.: Human Brain Mapping<sup>78</sup>



**Figure 2. DMN connectivity and social dysfunction in MDD patients.** The left panel depicts anterior (A), superior (B), and medial (C) views of the DMN (yellow-orange), along with its rmPFC and pSFG subregions (blue) that showed diminished connectivity in MDD patients with high vs. those with low social dysfunction (*TFCE & FWE corrected,  $P<0.05$* ). The rmPFC effect site is depicted in figure C and the pSFG site in figures A & B, with black edged circles marking the effect sites for better visibility. The yellow-orange scalar bar represents connectivity strengths (*Z-value*) within DMN, while the blue scalar bar reflects significance level of between-group differences in DMN connectivity (*P-value*). The distribution plot (middle panel, D) provides a quantitative visualization of this categorical between-groups effect, wherein mean connectivity estimates from the DMN effect sites (y axis) are plotted for each group separately (x axis). Exploratory dimensional analysis focusing on effect sites from the categorical analysis (i.e., parts of the rmPFC and pSFG), revealed the same pattern of diminished DMN connectivity as a function of higher social dysfunction levels across participants (*TFCE & FWE corrected,  $P<0.05$* ). The scatter plot (middle panel, E) provides a quantitative visualization of this effect, wherein mean connectivity estimates from the DMN effect sites (y axis) are plotted against social dysfunction composite scores (x axis). The black line depicts the slope of the association, with the grey bands indicating the 95% confidence interval of the slope. DMN = Default Mode Network; MDD = Major Depressive Disorder; rmPFC = Rostromedial Prefrontal Cortex; pSFG = Posterior Superior Frontal gyrus; *TFCE* = Threshold Free Cluster Enhancement; *FWE* = Family-Wise Error.

rather than individual questionnaires. Moreover, when we reran our connectivity analyses using the total sum scores of each social dysfunction questionnaire (both separately and in one model), no significant DMN effects emerged, and none of the questionnaires' total sum score was predictive of DMN connectivity strength in the effect sites documented here (*TFCE* & *FWE* corrected,  $P$ 's > 0.20). These findings thus cautiously hint that the cumulative social dysfunction index is ostensibly better able to pick up subtle brain-behavior relations, at least in this specific dataset, which echoes to some extent the current understanding on the topic.<sup>4</sup>

## DISCUSSION

The current study explored the relation between social dysfunctioning (operationalized as a composite of loneliness, perceived disability and small social network) and DMN whole-network connectivity among MDD patients. The analyses cautiously linked greater social dysfunctioning among MDD patients to diminished DMN connectivity, specifically within the rmPFC and pSFG. These preliminary findings pinpoint DMN connectional alterations as potentially germane to social dysfunction in MDD, and may as such improve our understanding of the underlying neurobiology.

### DMN Connectivity and Social Dysfunction

One of the key findings of this study is diminished connectional integrity of the DMN within its rmPFC subregion among MDD patients with more severe social dysfunction. This finding builds upon prior research suggesting that DMN connectional integrity is not only indispensable to adaptive human social functioning<sup>10,11,15</sup>, but also to positive social interaction.<sup>43</sup> It furthermore echoes findings in other neuropsychiatric disorders also characterized by severe social deficits (i.e., schizophrenia, autism), wherein diminished DMN connectivity with its rmPFC node similarly relates to more severe social dysfunctioning.<sup>12,44</sup> Of note, disruptions across multiple brain networks with the rmPFC as the core region are reported in MDD patients, and tentatively implicated as a key pathological feature of the disorder.<sup>22,23</sup> The rmPFC region is a key node of the DMN core system and mainly supports self-relevant sociocognitive and socioaffective processes.<sup>14,15</sup> The rmPFC, as part of the DMN, is for instance activated when one's memory is employed to construct future social scenes<sup>45</sup>, and also supports emotion regulation by drawing on past experiences.<sup>10</sup> The rmPFC is also implicated in the so-called "extended social affective default network", which supposedly governs various aspects of higher-order socioaffective information processing.<sup>46</sup> The rmPFC as part of the DMN core system is also crucially involved in coupling between DMN

subsystems, which allows for complex interactions and parallel functioning.<sup>15</sup> Connectional disturbances in the rmPFC part of the DMN may therefore not only upset functions tightly coupled to this subregion, but also prompt disruptions across DMN subsystems and their associated functions. This certainly fits the behavioral profile of most MDD patients, wherein a host of social dysfunctions tend to surface, ranging from biased self-related processing and social cognition to impaired interpersonal function.<sup>3,4</sup> These social deficits moreover contribute to greater MDD severity<sup>3,4</sup>, thus further highlighting the relevance of maladaptive social processing to MDD clinical presentation. Taken as a whole, our finding seems to suggest that diminished DMN connectivity, specifically within its rmPFC subregion, may carry relevance for a wide range of social deficits among more socially dysfunctional MDD patients. Future studies are warranted though to further explore and validate our tentative finding and interpretations, given the complexity of the DMN system and its modulation of intricate human social behavior.

We also found diminished DMN connectivity within the pSFG subregion among the more socially dysfunctional MDD patients. The pSFG is a posterosuperior PFC region that borders the precentral gyrus, and is bounded laterally by the superior frontal and cingulate sulci.<sup>47</sup> The pSFG is reckoned as a node within the dorsal medial DMN subsystem, and within this role supportive of interpersonal sociocognitive processes such as mentalizing and theory of mind (ability to understand others' intentions/emotions/beliefs/desires).<sup>14,15,48</sup> One may thus speculate that adverse connectional changes in this specific DMN subregion as documented here, could reflect biased mentalizing and theory of mind processes critical to adaptive social function. Depressed patients do in some cases indeed show deficits in these sociocognitive processes<sup>3,4,49,50</sup>, which apparently are to some extent driven by functional anomalies in brain regions that partly fall within the dorsal medial DMN subsystem.<sup>3,4</sup> Of note, more severe mentalizing and theory of mind deficits seemingly also predict increased MDD severity<sup>3,4,49</sup>, which again underscores the importance of impaired social functioning to less favorable MDD clinical presentation. It is interesting that mentalizing and theory of mind deficits in other neuropsychiatric disorders also seem to coincide with altered DMN connectivity with its pSFG subregion.<sup>12,51,52</sup> In sum, our finding may cautiously link altered pSFG connectivity within the DMN to suboptimal interpersonal and social interactive processing in more socially dysfunctional MDD patients. Further investigation and future replication of our finding is warranted though, as within the context of DMN, the contributions of pSFG to (mal)adaptive social processing are still understudied in MDD.

## Categorical versus Dimensional Approach

Social dysfunction and MDD are two intertwined and extremely complex phenomena that seem notoriously difficult to capture along one dimension or methodology<sup>4</sup>. Solely a categorical or dimensional examination of these two intertwined phenomena would likely lead to a fractured understanding of them and cause loss of information. Following this perspective and consonant with an increasing number of recent studies<sup>27–30,53</sup>, both categorical and dimensional analyses were performed to study the association between social dysfunctioning and DMN connectivity among MDD patients. The dimensional analysis tested whether a linear association could be found between individual participant's composite score and DMN connectivity across participants (i.e., significant slope across group), while the categorical analyses explored whether DMN connectivity differed between the high and low social dysfunction groups (i.e., different slopes for each group). The categorical analyses revealed diminished DMN connectivity among MDD patients with more severe social dysfunctioning. Whole-DMN dimensional analyses similarly revealed a pattern for reduced DMN connectivity as a function of more social dysfunctioning, though this effect did not pass statistical significance. Exploratory dimensional analysis did show that these patterns more prominently echoed that of the categorical analysis, when adopting a more lenient threshold ( $P < 0.001$ , uncorrected), or utilizing a region of interest approach. The exploratory nature of these post-hoc analyses, however, does warrant cautious interpretation, as they mainly served to aid transparency and completeness. The distribution of data and amount of variance across participants vs. within groups, the possibility of ceiling effects, and differences in statistical power may explain the subtle differences in outcomes of the categorical vs. dimensional analyses. In addition, one should consider the possibility that contrasting the extremes (as in categories) may better pick up subtle brain-behavior effects, then when enforcing a linear trend that in reality is subthreshold or perhaps not linear in nature. Yet, taken as a whole, both approaches seem to converge on the same pattern by cautiously linking more severe social dysfunctioning among MDD patients to diminished DMN connectivity. Nonetheless, the preliminary nature of the findings and interpretations do necessitate replication and further exploration to fully appreciate their relevance.

## Limitations and Strengths

The cross-sectional and exploratory nature of this study does not allow for firm causal inferences, and longitudinal research in preferably larger samples is warranted to tackle this limitation. The current study employed a composite index of social dysfunction among MDD patients, which notwithstandingly has its merits as mentioned earlier, but in essence remains a subjective proxy for social disability.

Social processing and functioning are multifaceted and complex phenomena, which are hard, if not impossible, to capture and reduce to a numerical value. A more in-depth examination of the composition of social networks or the nature of perceived social disability and loneliness are promising avenues for future research. In the end, the dissection of a complex phenotype such as social dysfunction requires the assessment of as much as possible putative contributors.<sup>4</sup> Although the used questionnaires are validated and specifically developed to study different aspects of social dysfunctioning, a more objective approach of social dysfunctioning would be valuable in complementing subjective self-assessments. However, the NESDA cohort study, from which we include a subset of participants, simply lacks more objective measures. The use of more objective measures is therefore beyond the scope of this paper. Validated questionnaires specifically developed to study different aspects of social (dys)functioning were used instead. This study moreover has a within-patient design, with all participants with depression likely experiencing some degree of low confidence within the social domain, as this is a disease-inherent feature. This lack of social confidence, however, should not be seen as an additional source of bias in their self-reported social (dys)functioning. The current study and its findings should thus ideally serve as a point of departure or source of hypothesis generation for more in-depth examination of social dysfunction and its biobehavioral underpinnings in the future. We additionally did not include healthy controls in the analyses, as the main objective was to probe the association between social dysfunction and DMN connectivity specifically and exclusively in MDD patients. While some in the field may deem this a potential limitation, an increasing number of seminal studies on MDD neurobiology are employing this within-patient methodology (e.g.,<sup>54,55</sup>), for it may aid the interpretability of findings. This is especially true in situations wherein explanatory and criterion variables of interest both tend to systematically differ between MDD patients and healthy participants (e.g., differences in general neurobiology, range of social dysfunction, clinical and sociodemographic characteristics). Simply correcting for these factors does not fully eliminate their confounding impact, thus rendering the interpretation of findings more arduous. Moreover, the topological architecture of the DMN can be reliably and consistently represented across populations<sup>40,56</sup>, making the inclusion of healthy controls for the current investigation not a prerequisite. In addition to above-mentioned limitations, it should be noted that the NESDA study excludes patients using non-SSRI antidepressants, which may introduce a selection bias and plausibly mitigate the generalizability of the findings.

Notwithstanding these limitations, our study also has several strengths worth mentioning. It is one of the first studies that explicitly aimed to unravel the neurobiological underpinnings of social dysfunction in MDD. This is of relevance,

as social dysfunction has been studied and established in various ways in MDD<sup>7,9</sup>, though a complete and integrated understanding of the underlying neurobiology is still lacking.<sup>3</sup> The sample is moreover very well described and rather homogeneous in terms of clinical presentation, with the high and low social dysfunction groups being not much different on key clinical parameters. We also corrected for relevant clinical and sociodemographic factors, which collectively aid the reliability of the study findings.

## Conclusions

In summary, our preliminary findings cautiously link greater social dysfunctioning among MDD patients to diminished DMN connectivity, specifically within its rmPFC and pSFG subregions. The findings seem to provide relevant, yet preliminary, clues on the neurobiology underlying social dysfunction in MDD, by highlighting DMN connectional disturbances as a potentially important factor. These initial exploratory findings should be further explored and validated, ideally through multimodal examination of DMN connectivity and complex network analyses (e.g., graph theory), to attain a more fine-grained representation of DMN and its network dynamics. The current findings could plausibly serve as a point of departure or source of hypothesis generation for these future endeavors.

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## Chapter 5

# Social Dysfunction is Transdiagnostically Associated with Default Mode Network Dysconnectivity in Schizophrenia and Alzheimer's Disease

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## ABSTRACT

**Objectives** Social dysfunction is one of the most common signs of major neuropsychiatric disorders. The Default Mode Network (DMN) is crucially implicated in both psychopathology and social dysfunction, although the transdiagnostic properties of social dysfunction remains unknown. As part of the pan-European PRISM (Psychiatric Ratings using Intermediate Stratified Markers) project, we explored cross-disorder impact of social dysfunction on DMN connectivity.

**Methods** We studied DMN intrinsic functional connectivity in relation to social dysfunction by applying Independent Component Analysis and Dual Regression on resting-state fMRI data, among Schizophrenia (SZ;  $N=48$ ), Alzheimer Disease (AD;  $N=47$ ) patients and healthy controls (HC;  $N=55$ ). Social dysfunction was operationalized via the Social Functioning Scale (SFS) and De Jong-Gierveld Loneliness Scale (LON).

**Results** Both SFS & LON were independently associated with diminished DMN connectional integrity within rostromedial prefrontal DMN subterritories ( $p_{corrected}$  range=0.02-0.04). The combined effect of these indicators (Mean.SFS+LON) on diminished DMN connectivity was even more pronounced (both spatially and statistically), independent of diagnostic status, and not confounded by key clinical or sociodemographic effects, comprising large sections of rostromedial and dorsomedial prefrontal cortex ( $p_{corrected}=0.01$ ).

**Conclusions** These findings pinpoint DMN connectional alterations as putative transdiagnostic endophenotypes for social dysfunction, and could aid personalized care initiatives grounded in social behavior.

## INTRODUCTION

Adaptive social functioning is critical to human survival and heavily dependent on complex neurocognitive systems unique to human beings.<sup>1-3</sup> Social dysfunction is accordingly one of the first and most common signs of major neuropsychiatric disorders. This is likely because of the enormous amount and complexity of brain network processes required to initiate and maintain adaptive social behavior.<sup>2,3</sup> Stimulated by clinical observations, converging lines of research report shared negative symptomatology such as social dysfunction across multiple neuropsychiatric disorders.<sup>2,4-6</sup> This advocates for a neurobiological correlate at the basis of social dysfunction that is possibly distinct and partly independent of the current neuropsychiatric nosologies.<sup>2,7</sup> Empirical data in support of this notion, however, is lacking and this tends to preclude a thorough understanding of social dysfunction as a transdiagnostic phenotype rather than a symptom of psychiatric nosologies.<sup>4,8</sup> To this end, the pan-European PRISM (Psychiatric Ratings using Intermediate Stratified Markers) project examined the cross-disorder value of social dysfunction and its putatively distinct neurobiological correlates in two distinctive disorders, Schizophrenia (SZ) and Alzheimer's Disease (AD).<sup>9</sup> Whereas these two disorders differ in core symptoms, genetic profile, and underlying neurobiology, they importantly overlap considerably in social deficits (i.e., social withdrawal, interpersonal dysfunction, loneliness)<sup>10,11</sup>. This renders them therefore as ideal candidates to address the PRISM study objectives. Using distinctively different neuropsychiatric disorders mitigates confounding effects and allows identification of *truly* transdiagnostic effects/associations.<sup>9</sup> This aligns nicely with the RDoC perspective that clinical psychological problems are best defined along functional domains with shared neurobiological substrates, regardless of diagnostic nosologies, to attain novel insights and advance treatment.<sup>4</sup>

A neurobiological system potentially relevant to both social (dys)function and SZ/AD pathophysiology is the brain's Default Mode Network (DMN), which crucially shapes various aspects of human social behavior.<sup>12-22</sup> The complexity of DMN function is reflected by the broad scope of brain areas involved in the DMN.<sup>12,13,23,24</sup> The core DMN system mainly processes personally relevant, sociocognitive information, with the rostromedial prefrontal cortex (PFC) and posterior cingulate cortex being its key nodes.<sup>12,13,23,24</sup> The medial temporal section of DMN is associated with recollection of experiences and autobiographical processing, and is comprised of the hippocampal formation, retrosplenial cortex, inferior parietal lobule, and ventromedial PFC.<sup>12,13,23,24</sup> The dorsomedial section of DMN, on the other hand, is predominantly involved in socially-colored, meta-cognitive processes and mentalizing (i.e., inferences about others' internal state), and is anchored in the

temporoparietal junction (TPJ), superior frontal gyrus (SFG) and dorsomedial PFC.<sup>12,13,23,24</sup> DMN sub-sections are highly intertwined and this allows for whole-network parallel functioning, which is a key ingredient to DMN modulation of complex human social behaviors.<sup>23</sup> Crucially, the DMN largely overlaps with the so-called “social brain”, for which perturbations among SZ/AD patients have been suggested and linked to social impairment.<sup>2</sup>

Alterations in DMN connectional integrity among SZ and AD patients have been described per disorder in several overview papers, and linked to deficits in social, cognitive, and affective processes that the DMN seems to subserve (e.g., self-referential processing, mentalizing, emotion recognition/resonance).<sup>2,18–22,25</sup> The most consistent finding in both SZ and AD is altered functional connectivity patterns within and between cortical midline sections of the DMN.<sup>2,18–22,25–27</sup> Of note, DMN disturbances are also observed in other neuropsychiatric disorders characterized by severe social dysfunction, including autism, social phobia, and depression<sup>17,28–32</sup>, further corroborating the importance of DMN to both normal and disturbed social functioning. It is assumed that large-scale brain network dysregulations, particularly those in the DMN, may contribute to core deficits in social, general cognitive, and affective functions, which in turn, could trigger (pre) clinical symptomologies in neuropsychiatric disorders such as SZ and AD.<sup>33</sup> Hence, a brain network approach towards social dysfunction in these distinct disorders offers a powerful means to transdiagnostically investigate how dysfunctional brain architecture could interfere with adaptive social behavior. Suboptimal DMN integrity has indeed been reported in relation to general social dysfunction as well as subjective feelings of loneliness.<sup>34,35</sup> Most convincing piece of evidence in this regard was recently presented in the massive UK Biobank dataset ( $N \sim 38000$ ), which robustly linked DMN dysconnectivity to subjective feelings of loneliness.<sup>14</sup>

Yet, no study has thus far directly examined the association between social dysfunction and DMN connectional integrity across SZ/AD patients and matched healthy controls. As such, we lack an integrated account of underlying mechanisms or a consensus regarding the framework of these relationships. The current study hence innovatively addressed this issue, by examining whether DMN connectivity is transdiagnostically coupled with social dysfunction, both its behavioral component and subjective experience, as these are often observed in SZ/AD patients and tend to co-occur with DMN disintegrity.<sup>2,34,35</sup> Diagnostic nosologies were accounted for in all analyses to identify truly transdiagnostic effects. Key clinical and demographic variables were corrected for to further aid robustness and specificity of findings. Importantly, all data collection (including MRI) and participant-level assessments were performed according to *fully harmonized* protocols across sites. We aimed to

include patients with a relatively recent disease onset in order to capture as much as possible of the underlying neurobiology of *social dysfunction* rather than long-term consequences of psychopathology or neurodegeneration. Post-hoc analyses additionally examined whether any brain-behavior relationship documented here is specific/exclusive to the DMN. Based on prior work on DMN and social (dys) functioning, we hypothesized social dysfunction to transdiagnostically relate to diminished DMN connectional integrity, especially within its cortical midline sections.<sup>2,18–22,25,31</sup> We also anticipated these effects to be distinct and (partly) independent of that of diagnostic status.<sup>2</sup>

## METHODS AND MATERIALS

### Participants

Data for the current study were derived from the PRISM study and included 48 SZ and 47 AD patients, along with 55 matched HC participants (28 HC younger (18–45 years) and 27 HC older (50–80 years)).<sup>10,36</sup> Participants were recruited between April 2017 and April 2019 from three sites in the Netherlands (University Medical Center Utrecht, VU University Medical Center, and Leiden University Medical Center) and two sites in Spain (Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa). Table 1 provides an overview of participant inclusion per site. Importantly, all data collection and participant-level assessments were performed according to *fully harmonized* protocols across sites. All participants provided verbal and written informed consent prior to participation, and were considered as sufficiently competent to participate by researchers and caregivers.

### Clinical Assessment

DSM-IV diagnosis of SZ was confirmed using the Mini-International Neuropsychiatric Interview (M.I.N.I.-screen), with at least 1 psychotic episode and maximum of 15-year disease duration since diagnosis.<sup>37</sup> SZ patients had to be on stable antipsychotic/anticholinergic/antidepressant medication dosage for at least 8 weeks, and 18–45 years of age. SZ patients were excluded if they scored  $\geq 22$  on the 7-item positive symptoms subscale of the PANSS, to rule out an active psychotic episode possibly hampering adequate study participation.<sup>36,38</sup> Diagnosis of probable AD was established according to the National Institute on Aging and the Alzheimer’s Association criteria.<sup>39</sup> AD patients had to additionally score 20–26 (i.e., mild AD pathology) on the mini-mental state examination (MMSE), and be 50–80 years of age.<sup>40</sup> AD patients with history of strokes, either based on clinical judgement, medical history or imaging results, were excluded. As the patient groups differed significantly in age, we also included two age-matched healthy

control groups in the study to mitigate age effects, while additionally correcting for age and age-squared in all analyses. HC participants exclusion criteria were any history of psychopathologies (as confirmed by the MINI) or neurological disorders, and usage of psychotropics and central nervous system affecting medication. More detail regarding participant in- and exclusion criteria is provided in the Supplement. Cognitive dysfunction was estimated in AD patients using the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog).<sup>41</sup> Current states of positive and negative symptoms of schizophrenia were measured using the PANSS (positive and negative syndrome scale).<sup>38</sup>

### Indicators of Social Dysfunction

The current study examined both the behavioral component and subjective experience of social dysfunction.<sup>29,30</sup> The behavioral aspect of social dysfunction was indexed with the Social Functioning Scale (SFS).<sup>42</sup> The SFS multidimensionally examines social functioning with seven subscales: social withdrawal, interpersonal functioning, prosocial activities, recreational activities, competence and performance independence and employment. The subscale 'employment' was not used for total scale analyses, since most participants were retired in the older HC and AD group introducing a bias in line with reporting in a previous study.<sup>43</sup> All subscales had different raw maximum scores ranging from 18-39. Questions were largely quantitative in nature such as: '*how often do you go to...*'. We reverse scored the individual subscales so that a higher score would indicate more social dysfunction. The total score on the SFS, following the original SFS scoring guidelines with provided conversion table, was used for the final imaging analyses.<sup>42</sup> The Jong-Gierveld Loneliness (LON) questionnaire was employed to assess the subjective experience of social dysfunction in the form of feelings of loneliness, with higher total scores indicating more loneliness, with questions such as: '*do you have someone in whom you can confide...*'.<sup>44</sup> The LON questionnaire consists of 11-items scored on a 3-point Likert scale, with a maximum score of 33. The two questionnaires were moderately correlated (Spearman's  $r = 0.54$ ,  $p < 0.001$ ), suggesting that while having some overlap they capture partly different aspects of social dysfunction. We also examined the average cumulative effect of the behavioral aspect and subjective experience of social dysfunction (Mean.SFS+LON) on DMN connectional integrity.

### MRI Data Acquisition and Preprocessing

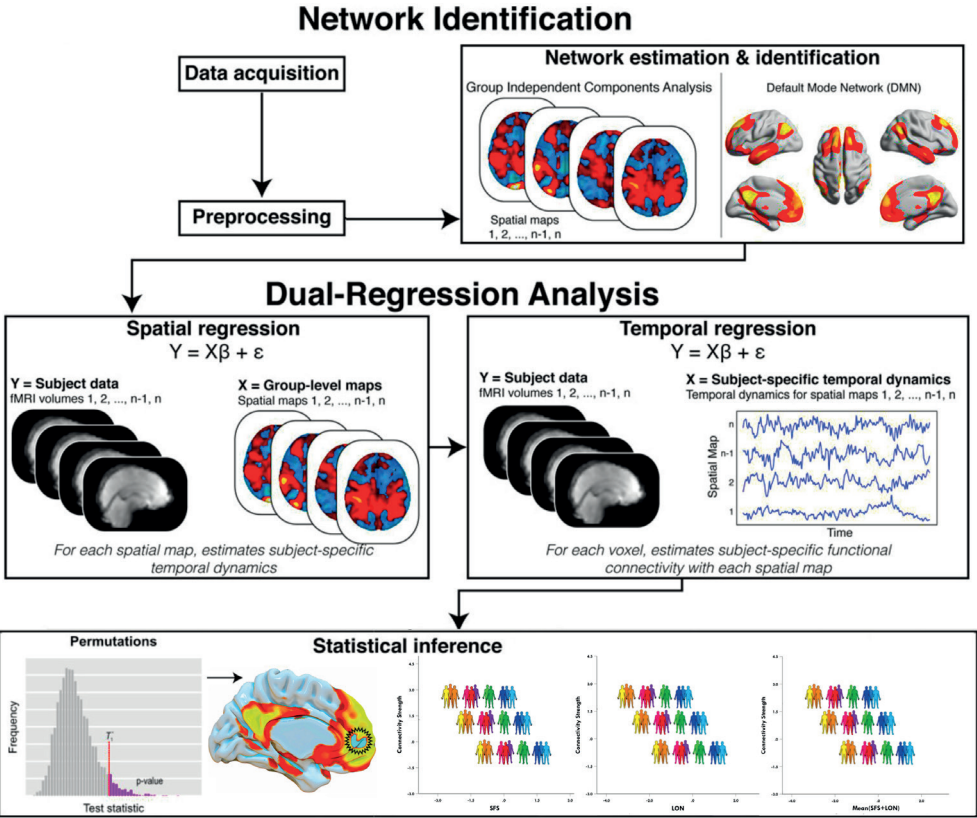
Resting-state fMRI and structural MRI data were acquired according to fully harmonized protocols across sites (see Supplement). Philips Achieva 3T MRI scanners were used at the Dutch sites, while a Siemens Prisma 3T MRI scanner was used at the Spanish site. All MRI assessments for both Spanish recruiting sites were performed on a single MRI scanner. An extensive quality assurance protocol was

implemented to mitigate any scanner-specific effects, which included harmonized scanning protocols, pilot testing with a "traveling head", and correction for site in all statistical analyses (see Supplement for details.) All data were subsequently preprocessed and cleaned according to established protocols and current standards, using FSL software (V6.0; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>, see also Supplement). Additional (micro)motion-related artefact removal (ICA-AROMA), and white matter/cerebrospinal fluid signal removal was implemented to further eliminate noise.

### DMN Functional Connectivity and Social Dysfunction

Figure 1 depicts the analytical pipeline employed in this study, with detailed description provided in the Supplement. In short, probabilistic Independent Component Analysis (ICA) within FSL's MELODIC module was used for data-driven decomposition of the entire preprocessed RS-fMRI dataset into 20 temporally and spatially independent components (i.e., intrinsic functional brain networks).<sup>45</sup> This level of granularity is typically used to identify large-scale, canonical brain networks.<sup>46,47</sup> The group-average set of components (i.e. resting state networks) generated by MELODIC was then used to generate subject-specific versions of them (spatial maps and associated time courses) via FSL's Dual Regression tool.<sup>45</sup> The DMN was identified based on its distinct topological architecture, as described in seminal overview papers and subjected to further analysis (Figure 1).<sup>46,47</sup>

We explored the transdiagnostic effects of social dysfunction on DMN whole-network connectivity, using non-parametric, permutation-based General Linear Model (GLM) analyses with FSL's Randomise tool (5000 permutations). The GLM included the individual participants' SFS (i.e., behavioral social dysfunction) and LON (i.e., subjective experience social dysfunction) total scores as separate regressors, wherein both the unique and as well as the average cumulative effects of these two constructs on DMN connectional integrity were examined. This dimensional analysis tested whether across the sample any linear associations can be found between DMN connectivity and individual participant's SFS and/or LON scores. Diagnostic status (i.e., SZ/AD/HC-younger/HC-older) was also entered in the GLM as regressor, in order to correct for it and disentangle its impact on DMN from that of social dysfunction. Key clinical (psychotropic medication, comorbid symptomology) and sociodemographic (age, age squared, sex, education, scan site/type) factors were corrected for in the analyses to aid robustness and reliability of findings (added as regressors in GLM). All variables were demeaned across groups, with statistical thresholding and correction for multiple comparisons achieved through Threshold-Free Cluster Enhancement (TFCE) with family-wise error (FWE) correction at  $p < 0.05$ .<sup>48</sup>



**Figure 1. Functional connectivity analyses of the Default Mode Network (DMN).** Collected resting-state fMRI data were first preprocessed and cleaned. Data from all participants was concatenated across time and submitted to a probabilistic group independent component analysis (ICA) using MELODIC. The group ICA produced a set of 20 independent spatial maps/components (i.e., functional networks). The set of spatial maps generated by MELODIC was then used to generate subject-specific versions of these spatial maps, and associated time courses, using Dual Regression. That is, for each subject, the group-average set of spatial maps was regressed (as spatial regressors in multiple regression) onto the subject's 4D space-time dataset. This resulted in a set of subject-specific time series, one per group-level spatial map. Next, these time series were regressed (as temporal regressors, again using multiple regression) against the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. Our component of interest (i.e., DMN) was then selected based on spatial similarity to functional networks described in prior seminal papers on DMN connectivity and architecture. Finally, permutation testing ( $N = 5000$ ) was used to examine the association between DMN connectivity and social dysfunction proxies, while correcting for key clinical and sociodemographic factors. Results were adjusted for multiple comparisons using Threshold-Free Cluster Enhancement with Family-Wise Error correction at  $P < 0.05$ . Adapted and reprinted with permission from Wiley Periodicals, Inc.: Human Brain Mapping<sup>85</sup>

**Table 1. Baseline characteristics (N=150)**

|                                                                    | Total sample<br>N=150 | Schizophrenia patients<br>N = 48 | Young healthy controls<br>N = 28 | Alzheimer's disease patients<br>N=47 | Old healthy controls<br>N =27 | p-value |
|--------------------------------------------------------------------|-----------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------|---------|
| <b>Demographics</b>                                                |                       |                                  |                                  |                                      |                               |         |
| Age (years), mean (SD)                                             | 48.7 (20.2)           | 30.8 (6.5)                       | 29.0 (7.4)                       | 68.4 (7.3)                           | 66.8 (7.0)                    | 0.34    |
| Sex (% female)                                                     | 37.3%                 | 27.1%                            | 39.3%                            | 41.7%                                | 48.1%                         | 0.52    |
| Education (years), mean (SD)*                                      | 15.6 (4.3)            | 15.1 (3.9)                       | 17.2 (2.6)                       | 14.5 (4.8)                           | 16.6 (4.9)                    | 0.19    |
| <b>Number of individuals per scan-site</b>                         |                       |                                  |                                  |                                      |                               |         |
| - UMC Utrecht                                                      | 20                    | 12                               | 3                                | 0                                    | 5                             |         |
| - Amsterdam UMC                                                    | 54                    | 11                               | 8                                | 25                                   | 10                            |         |
| - Leiden UMC                                                       | 16                    | 5                                | 3                                | 2                                    | 6                             |         |
| - Ruber International Hospital Madrid                              | 60                    | 20                               | 14                               | 20                                   | 6                             |         |
| <b>Specific disorder characteristics</b>                           |                       |                                  |                                  |                                      |                               |         |
| <b>Psychotropic medication</b>                                     |                       |                                  |                                  |                                      |                               |         |
| Antipsychotic (%)                                                  | 30.0%                 | 89.4%                            | 0.0%                             | 4.3%                                 | 0.0%                          |         |
| Antidepressant (%)                                                 | 12.0%                 | 20.8%                            | 0.0%                             | 17.0%                                | 0.0%                          |         |
| Acetylcholinesterase inhibitor and/or NDMA receptor antagonist (%) | 14.0%                 | 0.0%                             | 0.0%                             | 44.7%                                | 0.0%                          |         |
| Benzodiazepines (%)                                                | 8.0%                  | 12.5%                            | 0.0%                             | 8.5%                                 | 7.4%                          |         |
| Other psychotropics (%)                                            | 6.0%                  | 14.6%                            | 0.0%                             | 2.1%                                 | 3.7%                          |         |
| <b>Severity of disorder</b>                                        |                       |                                  |                                  |                                      |                               |         |
| Schizophrenia severity, Positive symptoms, mean PANSS (SD)         | NA                    | 11.0 (3.5)                       | NA                               | NA                                   | NA                            |         |
| Negative symptoms, mean PANSS (SD)                                 | NA                    | 14.9 (6.1)                       | NA                               | NA                                   | NA                            |         |
| Alzheimer's disease severity, mean ADAS-Cog (SD)                   | NA                    | NA                               | NA                               | 26.8 (7.2)                           | NA                            |         |
| <b>Social dysfunction scores</b>                                   |                       |                                  |                                  |                                      |                               |         |
| Reversed SFS score                                                 | 21.1 (9.6)            | 29.2 (8.9)                       | 14.2 (5.0)                       | 21.8 (7.1)                           | 12.6 (4.9)                    | <0.001  |
| Loneliness score                                                   | 2.5 (3.1)             | 4.8 (3.9)                        | 0.5 (1.0)                        | 1.9 (2.1)                            | 1.3 (1.8)                     | 0.19    |

Chi-square tests were employed for categorical variables, and independent sample t-test for continuous variables. \*Non-parametric tests (Mann-Whitney for continuous variables) were conducted when assumptions were violated.

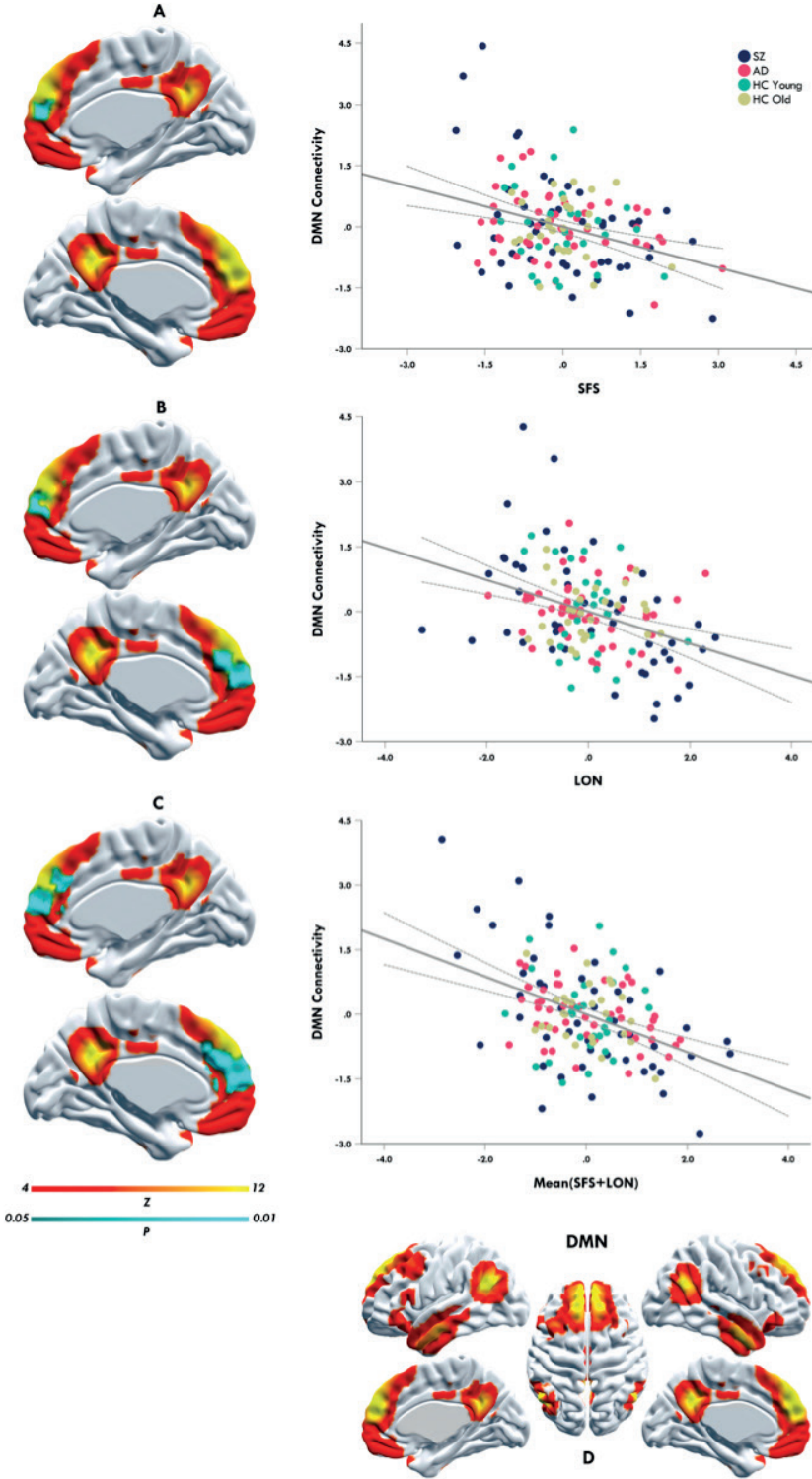
RESULTS

Sample Characteristics

The sample characteristics are listed in Table 1. As expected, a large majority of SZ patients used antipsychotic medication (89.4%), with some also using antidepressants (20.8%). Nearly half of the AD patients used AD-specific medication (e.g., Acetylcholinesterase inhibitor and/or NMDA receptor antagonist) (44.7%). Mean positive and negative symptoms in SZ patients was 11.0 and 14.9, respectively, as measured with the PANSS (indicating mild pathology, matching stable outpatient clinic characteristics). Mean dementia symptomatology was 26.8 on the ADAS-cog for the AD group (indicating mild dementia symptomatology). Compared to age-matched controls, patients had in general more depressive symptomatology and less positive affect, though none of the groups reached clinical depression levels, as participants with clinical depression were excluded before the analyses. The SFS and LON total scores differed between patient groups and their age-matched HC participants ( $p$ 's  $< 0.001$ ), except for LON scores between the AD patients and older healthy controls ( $p = 0.19$ ). The patient groups (AD and SZ patients) differed significantly in their SFS, LON and mean SFS+LON scores ( $p$ 's  $< 0.001$ ).

> **Figure 2. Social dysfunction transdiagnostically associated with DMN connectivity.** The upper panel (A) depicts medial views of the DMN (yellow-orange), with the effects site (rmPFC; blue) for the transdiagnostic negative association between DMN connectivity and the SFS superimposed on it (TFCE & FWE corrected,  $P = 0.02$ ). The middle panel (B) depicts medial views of the DMN (yellow-orange), with the effects site (rmPFC; blue) for the transdiagnostic negative association between DMN connectivity and LON superimposed on it (TFCE & FWE corrected,  $P = 0.04$ ). The lower panel (C) depicts medial views of the DMN (yellow-orange), with the effects site (rmPFC & dmPFC; blue) for the transdiagnostic negative association between DMN connectivity and Mean SFS+LON superimposed on it (TFCE & FWE corrected,  $P = 0.01$ ). The last panel (D) depicts the DMN constellation as generated per our resting-state fMRI pipeline. The yellow-orange scalar bar represents connectivity strengths (Z-value) within DMN, while the blue scalar bar reflects significance level ( $P$ -value) of social dysfunction-DMN associations. The scatter plots (A, B, C) provide a quantitative visualization of this effect, wherein mean connectivity estimates from the DMN effect sites (y axis) are plotted against social dysfunction scores (x axis). The values on y and x axis are Z-score residuals. The black solid line depicts the slope of the association, with the dotted bands indicating the 95% confidence interval of the slope. Higher positive values on the x axis indicate more severe social dysfunction.

SFS= Social Functioning Scale; LON = de Jong-Gierveld Loneliness questionnaire



## DMN Connectivity and Social Dysfunction

The analyses revealed a transdiagnostic association between behavioral aspects of social dysfunction (SFS) and diminished DMN connectional integrity, specifically within the rostromedial PFC subterritory of the DMN (*TFCE* & *FWE* corrected,  $p=0.02$ ) (Figure 2A). A similar link was found between participants' subjective experience of social dysfunction (LON) and diminished DMN connectional integrity in the rostromedial PFC (*TFCE* & *FWE* corrected,  $p=0.04$ ) (Figure 2B). The mean cumulative effect of SFS and LON on diminished DMN connectivity was even more pronounced (both spatially and statistically), comprising large sections of the rostromedial and dorsomedial PFC ( $p=0.01$ ) (Figure 2C). Post-hoc analyses additionally revealed that above-mentioned effects were not moderated (interaction) by diagnostic status ( $p's>0.05$ ), thus further corroborating their transdiagnostic nature.

On top of our transdiagnostic analyses of social dysfunction-DMN relationships, our GLM model simultaneously also investigated the impact of diagnostic status on DMN connectivity, so to fully appreciate the unique contributions of social dysfunction to DMN integrity. Of note, these analyses thus mainly serve as *sensitivity tests*, and were not set up to examine the DMN-correlates of SZ/AD diagnostic status (already described extensively).<sup>18,49</sup> The analyses showed that SZ patients exhibited abnormally increased DMN connectivity within rostromedial PFC and temporoparietal territories, in comparisons to their age-matched healthy control peers (*TFCE* & *FWE* corrected,  $p=0.01$ ) (see Figure S1 in Supplement). No differences were found in DMN connectivity between the AD patients and older HC participants. These disorder-specific findings (or their lack of) clearly diverge from those of social dysfunction, being spatially different and directionally distinctive (increased vs. decreased connectivity), further corroborating the specificity of the social dysfunction-DMN relations we documented.

## Network-Specificity Analyses

Post-hoc analyses assessed whether brain-social behavior relationships documented here are specific to the DMN. We therefore reran our dimensional brain-social dysfunction analyses, though now focusing on two other canonical brain networks often implicated in neuropsychiatric disorders: The Salience Network (SN; serves saliency mapping) and the Central Executive Network (CEN; governs executive functions & behavioral control). The influential triple network model of psychopathology posits that functional disorganization within the DMN and these two networks collectively spur susceptibility for maladaptive social behavior and mental disorders, including SZ and AD.<sup>50</sup> The SN and CEN were part of our 20 network MELODIC-ICA solution (see Methods), which automatically split up the CEN into a right- and left-lateralized network assembly. GLM modeling and

analytical sequence proceeded exactly as described for the DMN-social dysfunction analyses, though statistical inferences were additionally Bonferroni corrected for  $N$  networks to control for multiple testing (*TFCE* & *FWE*;  $P\ 0.05/3 = 0.017$ ). No significant link between social dysfunction and SN or CEN connectivity emerged though ( $P's>0.05$ ), indicating that the brain-behavior relationships reported here are specific to DMN.

## DISCUSSION

The current study examined how behavioral aspects and subjective experiences of social dysfunction transdiagnostically associate with DMN connectional integrity, among SZ/AD patients and age-matched healthy controls. We found that the behavioral aspect and subjective experience of social dysfunction are both transdiagnostically linked to decreased prefrontal DMN connectivity, with their cumulative effect being even more pronounced (both spatially and statistically). These effects were independent of diagnostic status, not confounded by key clinical (psychotropic medication, comorbid symptomology) and sociodemographic (age, sex, education, scan location) factors, and highly specific to the DMN. These findings pinpoint DMN connectional alterations as putative transdiagnostic endophenotypes for social dysfunction, and could plausibly aid personalized care initiatives grounded in social behavior.

## DMN Connectivity and Social Dysfunction

Our analyses revealed that the behavioral aspect and subjective experience of social dysfunction are both uniquely and transdiagnostically associated with decreased DMN connectivity across SZ/AD/HC participants. The main effect site for this negative association comprised the rmPFC subsection of the DMN, and to a lesser extent its dmPFC subterritory. Findings largely echo the growing body of literature emphasizing that the DMN is central to adaptive social functioning.<sup>13,23,51–53</sup> Social dysfunction has recently been associated with decreased connectivity in the rmPFC as part of the DMN in various neuropsychiatric disorders,<sup>17,31,54</sup> though our study is the first to showcase this in a transdiagnostic sample. Although in close topological proximity, the rmPFC and dmPFC have differential functions within the DMN.<sup>15,55,56</sup> The rmPFC is a key node of the core DMN system in addition to the PCC,<sup>12,13,23</sup> and as such actively involved in coupling of the DMN subsystems. The rmPFC mainly functions within the core DMN system to support self-referential thoughts, self-other dichotomies, and socioemotional processing.<sup>12,13,23,56</sup> The core DMN system is active when constructing future scenes based on autobiographical experiences, as well as when we are thinking of friends and individuals similar to ourselves.<sup>23,57</sup> Data

on the rmPFC support the concept that self-referential processes are also employed for thinking about others.<sup>57</sup> The dmPFC on the other hand is part of the dorsomedial DMN (dmDMN) subsystem, which additionally comprises the TPJ and SFG.<sup>24,56,57</sup> The dmDMN subsystem is predominantly active during higher order social processes such as self-reflective judgements, or when we are inferring upon the mental states of others (i.e. mentalizing).<sup>12,15,23</sup>

In this study, more severe social dysfunction (mean cumulative effect of behavioral and affective social dysfunction) was associated with more widespread perturbations in the DMN, with diminished recruitment of the dmPFC (i.e. dmDMN subsystem node) in addition to the rmPFC (i.e. core DMN node). This supports the notion that the connectional disturbances in the core DMN could lead to dysconnectivity in the dmDMN subsystem as well.<sup>7,23,29,31,33</sup> However, it remains unclear if social dysfunction gives rise to DMN dysconnectivity or the other way around. The cross-sectional nature of this study does not allow for causal inferences, yet tentative empirical data tends to support the DMN dysconnectivity as the causal factor. Clinical examples include rTMS and psychotropic medication that manage to normalize DMN functional and connectional integrity, followed by altered (more favorable) social behavior.<sup>21,58–61</sup> Moreover, animal data describing stimulation/manipulation of key DMN subregions/circuits moreover show stark changes in social behavior.<sup>5,62–66</sup> Additionally, top hits from a recently performed GWAS of the sociability trait were most heavily expressed in frontal DMN regions/circuits, with sociability and loneliness moreover being genetically linked.<sup>67</sup> Thus, irrespective of the origin of the perturbed functional connectivity within the DMN, disturbances in this crucial brain network appear to give rise to a wide variety of core deficits in sociocognitive and socioaffective functioning, which are likely to trigger (sub) clinical symptomatology.<sup>29</sup>

Our post-hoc analyses did not find any significant links between social dysfunction and SN or CEN connectivity ( $P$ 's > 0.05, Bonferroni corrected), which was performed to probe the specificity of DMN disintegrity to social dysfunction. This is somewhat in contrast to current literature on large-scale networks and human behavior or neuropsychiatry.<sup>50</sup> The Triple network model of psychopathology, for instance, postulates that an imbalance within or between large-scale brain networks could derail key cognitive and emotional processes. Specifically, the SN mainly seems to serve as a crucial switch from the internal oriented DMN with the more externally oriented CEN.<sup>33,68,69</sup> Whereas the DMN is directly linked to self-related and social processes, the SN seems to differentiate between internal and extra personal stimuli in order to guide (social) behavior. While the roles of the SN and CEN are notable in adaptive behavioral processes, findings from current and prior research indicate

that the DMN is highly specific for social dysfunction. This is most convincingly illustrated in the massive UK Biobank study (N~38000) where there was a link between impaired social behavior and the DMN, but no other brain network.<sup>14</sup>

## DMN Connectivity and Diagnostics

Though this study was not designed to replicate dysfunction previously well described changes in the DMN as a function of SZ or AD diagnosis, we did include categorical diagnostics in the model to pinpoint the unique transdiagnostic effect of *social dysfunction* on the DMN. This mainly served as a *sensitivity test*, and was not set up to examine the DMN-correlates of SZ/AD diagnostic status (described extensively elsewhere<sup>18,49</sup>). We found disorder-specific *increased* connectivity in the DMN among SZ patients relative to their HC peers, mainly in the TPJ and rostromedial PFC. Although inconsistencies exist in the field showing both hypo- and hyper-connectivity of the DMN in SZ patients, most evidence points towards hyperconnectivity of the DMN.<sup>19,20,22,25–27,70</sup> The TPJ, for example, seems to govern the balance between external and internal stimuli, between sensory information and social cognition or the mirror system.<sup>20,52,71–74</sup> An imbalance in this area might thus lead to altered integration of context-dependent information.<sup>74</sup>

Commonly described disruptions of the DMN within AD patients are located in the medial temporal lobe and posterior cingulate cortex/precuneus, spreading to the lateral parietal and medial frontal regions of the DMN as the disease progresses.<sup>75,76</sup> In contrast to these earlier findings, we found no dysconnectivity of the DMN in AD patients relative to their age-matched healthy controls. To reiterate, however, this study was not designed to replicate previously implicated changes in the DMN as a function of AD or SZ diagnosis. We only included categorical diagnostics in the model to pinpoint the unique transdiagnostic effects of social dysfunction on the DMN (over and above diagnostics), thus simply serving as a *sensitivity test* rather AD diagnostic correlates. Moreover, our relatively small and mildly impaired AD sample, along with the social dysfunction-oriented GLM models may have further contributed to this null finding.

The disorder-specific findings (or their lack of) clearly diverge from those of social dysfunction, being spatially different and directionally distinctive (increased vs. decreased connectivity). In short, while patient-status may affect DMN connectivity, it importantly does not account for the above-mentioned findings on social dysfunction-DMN coupling. In fact, our findings robustly showcase that DMN connectional changes are a neurobiological correlate of social dysfunction that is distinct and independent of current neuropsychiatric nosologies. Findings thus

support the ongoing paradigm shift from the traditional nosological perspective on neuropsychiatry towards a more transdiagnostic approach of key functional domains and their neurobiobehavioral underpinnings, such as social (dys)function.<sup>4,7</sup>

## Strengths & Limitations

Our study has a number of limitations that need to be acknowledged. For example, the cross-sectional nature of this study does not allow for causal inferences. Ideally, longitudinal studies with additional neuropsychiatric disorders (e.g., depression/anxiety) should further explore and validate the findings reported here. We examined the link between DMN connectional integrity and social dysfunction, as measured independently by two different questionnaires and their mean cumulative score. However, questionnaires remain a self-reported proxy for social dysfunction of which we know it to be different – at least to some extent – from the social dysfunction perceived by others.<sup>77,78</sup> The use of questionnaires to capture the notoriously complex phenomenon of social dysfunction is a vast simplification. However, to date it is the best proxy available for easily accessible and reliable assessments until more sophisticated techniques are employed in this population.<sup>79,80</sup> We included patients with a relatively recent disease onset and few comorbidities, in order to capture as much as possible the underlying neurobiology of social dysfunction rather than long-term consequences of psychopathology or neurodegeneration. Despite these efforts, we acknowledge that we cannot fully rule out such effects. We also did not specifically probe possible AD-specific grey matter atrophy, which is typical to more severe cases, whereas our AD patients had recent disease onset and few comorbidities. Moreover, it is good to highlight that the focus of the current paper is not on grey matter morphology but large-scale network functional connectivity, which is less susceptible to focal morphological atrophy. Our extensive image pre-processing pipeline and the data-driven network construction furthermore safeguard against confounding impact of many neurobiological features, including atrophy. In fact, the ICA/Dual Regression approach implemented here is strikingly apt in representing the topological architecture of the DMN in a *reliable and consistent* manner *across* various populations, irrespective of age, sex, or diagnostic status.<sup>46,81</sup> Finally, the current paper has a strong transdiagnostic approach and the link between DMN disintegrity and social dysfunction is seen *across* the groups, not just in the AD participants (see Figure 2). That is in fact the beauty and strength of modern transdiagnostic psychiatry, it aims to pinpoint neuro-bio-behavioral relations *independent* of diagnostic classifications and their respective sequelae.<sup>82,83</sup> Nonetheless, it is important to acknowledge that distinct neurobiological processes might underlie the link between DMN and social dysfunction in AD versus SZ patients. More specifically, while this link in AD patients may be propelled by DMN degeneration (i.e., loss of neuronal activity and

subsequent network dysfunction), in SZ patients this could be more akin to circuit imbalances and neurodevelopmental anomalies within the DMN. While beyond the scope of the current study, future research should address these issues, ideally by combining longitudinal task-based and resting-state fMRI measures of DMN integrity, so to grasp activity-connectivity interdependencies.

In spite of these limitations, the study certainly adds to our understanding of transdiagnostic social dysfunction and its putative neurobiology.<sup>4,10</sup> All data collection (including MRI) and participant-level assessments were moreover performed according to fully harmonized protocols across sites, and key clinical/sociodemographic factors corrected for, to boost robustness and reliability of our study results. We also ran network-sensitivity analyses, which reaffirmed that the documented social dysfunction effects are truly specific to the DMN. The study moreover has an innovative approach, combining two distinctive neuropsychiatric disorders with differing disease characteristics on the important topic of social dysfunction. Current findings on social dysfunction may therefore aid data-driven patient stratification initiatives given their transdiagnostic dimensional feature. Perhaps more importantly, these findings may also inform the development of more robust biomarkers and effective treatment strategies that are rooted in social behavior, and its neurobehavioral underpinnings.<sup>4,10</sup>

## Conclusions

In summary, our findings suggest that social dysfunction transdiagnostically associates with DMN connectional disintegrity across SZ/AD patients and healthy controls. These findings pinpoint DMN connectional alterations as putative transdiagnostic endophenotypes for social dysfunction, and could plausibly aid personalized care initiatives grounded in social behavior. These initial exploratory findings should be further validated, for example through multimodal examination of DMN connectivity and complex network analyses, to attain a more fine-grained understanding of DMN contributions to social (dys)function. The current findings could plausibly serve as a point of departure or source of hypothesis generation for these future endeavors.

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SUPPLEMENT

Recruitment of participants

Eligible patients were mainly identified via their health-care providers from the five recruiting sites in the Netherlands (University Medical Center Utrecht, VU University Medical Center, and Leiden University Medical Center) and Spain (Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa). Patients were also recruited via patient cohort registers from these sites and patient websites. Healthy controls were primarily recruited via different media such as flyers, posters and initiatives to support recruitment of healthy controls in scientific research (such as [www.hersenonderzoek.nl](http://www.hersenonderzoek.nl) in the Netherlands).

Before enrolling the individuals to the study, a verbal description was given by a member of the research team whilst shortly screening the possible participant. The study included 3 assessment days which started with verbal and written informed consent. First part of assessment day 1 was an extensive screening (including QIDS-SR16, MMSE, PANSS, M.I.N.I.-screen, handedness) to verify eligibility of the participants.<sup>32,33,68,69</sup> Clinician-Rated (IDS-C Second part of assessment day 1 included social functioning questionnaires. Assessment day 2 included the MRI and EEG assessments such as the resting-state scan. Assessment day 3 included again MRI and EEG tasks (different scans and paradigms). All MRI assessments of the Spanish participants were performed in the Ruber International Hospital Madrid. More in depth description of the implemented study protocol can be found elsewhere.<sup>3,32</sup> domain- or symptom-focused approaches have been heralded as advancing psychiatric research, but relatively few clinical research programmes have been undertaken to leverage their potential. In this manuscript we describe the approach and protocol for an exploratory study, PRISM (Psychiatric Ratings using Intermediate Stratified Markers

Additional in- and exclusion criteria

Additional cross-disorder patient exclusion criteria were: a) diagnosis of a severe, current Major Depressive Disorder (MDD) DSM-IV diagnosis (as assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I.-screen))<sup>32</sup> and with a Quick inventory of Depressive Symptomatology, Self-Rated (QIDS-SR)  $\geq 16$ <sup>68</sup>, b) diagnosis of any other *primary* psychiatric diagnosis that requires intervention; c) alcohol or drug abuse/dependence within previous 3 years (as assessed on the M.I.N.I.-screen), d) severe Parkinsonism as a consequence of antipsychotic medication (as assessed with a score  $\geq 4$  on the Extrapyramidal Symptom Rating Scale<sup>70</sup>, e) unstable comorbid somatic disorders potentially affecting the central nervous system (CNS), f) medication that could affect CNS (no stable dosage in last 8 weeks).

We included two HC groups, matching on sex and age with the SZ (between 18-45 years) and AD (between 50-80 years) groups. Scores on the MMSE for the older HC participants should be comparable to normative data according to age and years of education. Exclusion criteria for the HC groups were: a) history of psychiatric Axis-I disorder (as confirmed by the MINI) or neurological disease associated with cognitive impairment; b) mild or more severe depression (score  $>5$  on the QIDS-SR); c) currently or prior use of antidepressant or anxiolytic medication including benzodiazepines; d) prescribed medication in the last 6 weeks that may affect the CNS. All participants (patients and healthy controls) had to be right-handed or ambidextrous, free of any MRI contraindications, should be able to speak, read and write in the language in which psychometric tests are provided and should not be socially withdrawn due to external circumstances (lack of access to transport) or comorbid medical disorder (hearing loss, lack of mobility). Site staff was able to stop or postpone an assessment or specific tasks if, in their opinion, the participant was unable to complete an assessment (e.g. when the participant was fatigued, or unable to understand a specific task).

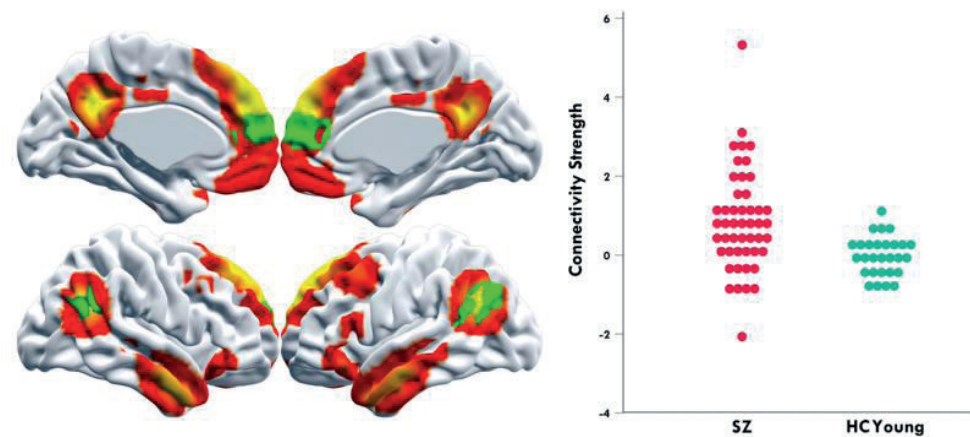
### Neuroimaging data acquisition, fMRI preprocessing and analyses

While the Dutch sites (Amsterdam, Leiden, Utrecht) all used a Philips Achieva 3-Tesla MRI scanner (32-channel head coil), the Spanish site (Madrid) employed a Siemens Prisma 3-Tesla scanner (64-channel head coil). To tackle any scanner-type effects, an extensive protocol was set up prior to the start of the actual inclusion phase to reassure consistency across scanners. This protocol indeed included fully harmonized MRI acquisition protocols, as well as pilot testing with a “traveling head” (a team member) who underwent the scanning protocol across the different scanners in the Netherlands and Spain. Data analyses of the “traveling head” revealed no site-specific effects, which allowed the actual data inclusion to commence. On top of these stringent quality assurance measures, all statistical analyses correct for site as a confounding factor. As such, we can confidently rule out major scanner-specific effects. The following scan parameters were used: 240 whole-brain volumes; repetition time (TR) 2000ms; echo time (TE) 30ms; flip angle 80°; 46 transverse slices; no slice gap; field of view (FoV) 240 x 240 mm for Philips scanner, 210 x 210 mm for Siemens scanner; in-plane voxel size 3.0 x 3.0 mm; slice thickness 3 mm; duration 8 min. An additional anatomical scan was performed for registration purposes and gray matter analyses with a sagittal 3-dimensional gradient-echo T1-weighted image (TR 2300 ms; TE 2.98 ms; flip angle 9°; 176 sagittal slices; no slice gap. FoV 256 x 256 mm; 1 mm isotropic voxels; duration 4.5 min for Siemens scanner; TR shortest; TE shortest; flip angle 8°; 170 sagittal slices; no slice gap. FoV 258 x 258 mm; 1 mm isotropic voxels; duration 5.3 min for Philips scanner). In the darkened MRI room participants

were instructed to lie still and look at the fixation cross displayed in the middle of the screen, without falling asleep. Participants confirmed wakefulness after the scanning session. To minimize between-site variance, a standardized/harmonized operating protocol was implemented, including the approach of the participants in and outside the scanner.

RS-fMRI data was preprocessed and cleaned according to established protocols, as implemented in FSL (FMRIB Software Library) version 6.0.<sup>71</sup> This comprised head motion correction to the middle volume using MCFLIRT, smoothing using a Gaussian kernel of 5 mm full width at half maximum; grand mean intensity normalization (to value 10000) of the entire 4D dataset by a single multiplication factor (i.e. 4D grand-mean scaling in order to ensure comparability between data sets at the group level); high pass temporal filtering (Gaussian-weighted least-squares straight line fitting with a 0.01 Hz).<sup>72</sup> The resulting RS-fMRI images were first aligned to the individual's high resolution T1-weighted anatomical image using FSL boundary-based registration (BBR), and subsequently to the MNI152 (Montreal Neurological Institute) standard space using FLIRT with 12 degrees-of-freedom, further refined using non-linear warping through FNIRT.<sup>71-74</sup> On top of this, (micro)motion-related artefact removal (ICA-AROMA), and white matter/cerebrospinal fluid signal removal was implemented to further clean the data of noise. Participants were excluded if head movement was above 4 mm or when the root-mean-squared of the framewise displacement exceeded 0.15, or if functional images were of insufficient quality. In total, MRI data was available for 159 participants, 8 were excluded because of excessive motion, and 1 because of poor imaging qualities, leaving 150 participants for the final imaging analyses reported on here.

Impact of SZ diagnostic status on DMN connectivity



**Figure S1.** DMN functional dysconnectivity in SZ as compared to age-matched healthy controls. Left depicts medial and lateral views of the DMN (yellow-orange) with SZ-specific DMN hyperconnectivity within the TPJ and rmPFC (green), in comparison to age-matched HC participants (*TFCE* & *FWE* corrected,  $p=0.01$ ). Right panel depict distribution plot to quantitatively visualize this categorical between-groups effect, wherein mean connectivity estimates from the DMN effect sites (green regions; y axis) are plotted for each group separately (x axis). The values on the y axis are Z-score residuals.

## Chapter 6

# General discussion

The general discussion of this thesis will begin with a summary of the findings of all chapters. This will be followed by a discussion of the answers to the two research questions. Strengths and limitations of the experimental design will be considered. Clinical implications and recommendations for future research will be discussed. Lastly, a conclusion on the subject of this thesis will be given.

## SUMMARY OF MAIN FINDINGS

We focused on the association of three different neuropsychiatric disorders (i.e. major depressive disorder (MDD), schizophrenia (SZ) and Alzheimer's disease (AD)) and social dysfunction (see figure 1) with the purpose of examining social dysfunction as a transdiagnostic phenotype. First, we examined the ways in which social processes may be similar or different in MDD, SZ and AD. To do this, we isolated behavioral and affective indicators of social dysfunction. Behavioral indicators are quantitative and objective, while the affective indicators being are qualitative and subjective. In **chapter 2**, we examined social functioning among 2952 NESDA-participants (healthy controls N=650, individuals remitted from anxiety and/or depressive disorder N=621, patients with anxiety disorder only N=540, depressive disorder only N=393 or comorbid anxiety and depressive disorders N=748) using affective and behavioral indicators. The available behavioral indicators of social dysfunction were: 1. the social network size (part of the Close Person Inventory), 2. the social activities (5 questions taken from the LASA study) and 3. social support (Close Person Inventory).<sup>1,2</sup> Affective indicators included 4. perceived social disability (the WHODAS 'getting along' domain), 5. loneliness (the de Jong-Gierveld Loneliness questionnaire), and 6. affiliation (the affiliation questionnaire).<sup>3-5</sup> We found significant social dysfunction in patients with anxiety disorders, and to an even higher degree in those with depressive disorders, and most prominently in patients with comorbid anxiety and depressive disorders. In addition, our study also showed that both affective and behavioral aspects of social dysfunction were compromised, with affective aspects being the more severely impaired in all groups as compared to healthy controls. The affective indicators loneliness and perceived social disability, in addition to the behavioral indicator social network size, showed the largest effect sizes for the patients with comorbid anxiety and depression, as compared to healthy controls (Cohen's *d* ranging from 0.81- 1.76). We also described that even after remission of affective psychopathology, residual impairments in social functioning tended to remain in social network size, social support, loneliness, and perceived social disability. Importantly, we also established that perceived social disability among patients is predictive of a depressive and/or anxiety diagnosis as much as two years later.

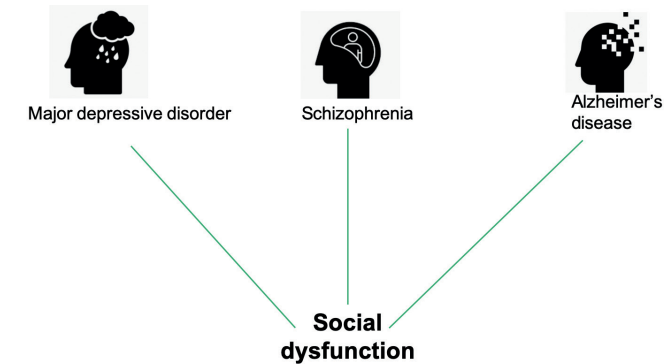
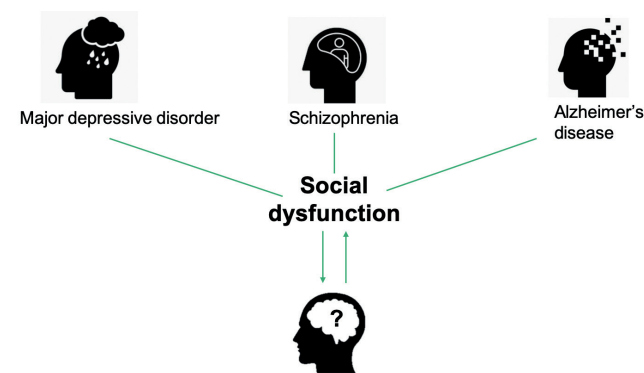


Figure 1: graphic overview of part I in this thesis in which we studied the differences and similarities of social dysfunction in MDD, SZ and AD.

**Chapter 3** describes social dysfunction in schizophrenia and Alzheimer's disease patients (N=164) using behavioral and affective indicators of social dysfunction. Building on the findings of the NESDA study described above, we used perceived social disability (the WHODAS 'getting along' domain) and loneliness (the de Jong-Gierveld Loneliness questionnaire) as affective indicators of social dysfunction, and we added a rater-perceived social disability questionnaire (also the WHODAS 'getting along' domain).<sup>3,4,6</sup> Raters included an intimate partner or other close family member, as well as a research staff member. The individual subscales of the Social Functioning Scale and its total score (SFS) were used as behavioral indicators of social dysfunction.<sup>7</sup> In this PRISM sample, both SZ (N=56) and AD (N=50) patients exhibited more social dysfunction when compared with age- and sex matched HC participants (HC younger N=29; HC older N=28). As compared to HC, both behavioral and affective social functioning were poorer in SZ patients (Cohen's *d*'s 0.81-1.69), whereas AD patients exhibited poorer behavioral social function (Cohen's *d*'s 0.65-1.14). Comparing the patient groups exclusively, we found that the behavioral aspects of social functioning were fairly similar, with the affective indices being less favorable for the SZ patients, who were found to have greater feelings of loneliness and perceived social disability than did the AD patients. Across patient groups, positive mood and lower levels of depression and anxiety were strong determinants of better social functioning, even more so than severity of disease indicators. Raters scored the perceived social disability of SZ and AD as equally impaired. This is in contrast to the lower levels of perceived social disability reported by the AD patients themselves as compared to the SZ patients, which may point to possible underreporting by AD patients.

Together, chapters 2 and 3 indicate that both behavioral and affective of social functioning are largely impaired in MDD, SZ and AD.

In the second part of this thesis, we explored the role of the Default Mode Network (DMN) in social dysfunction across different neuropsychiatric disorders (i.e. MDD/SZ/AD), as is illustrated in figure 2. **Chapter 4** examines whether DMN connectional integrity among MDD patients (N=74) covaries with individual scores on an integrated social dysfunction composite, composed of behavioral and affective features. Building on findings described above, we used the network size (part of the Close Person Inventory) as behavioral indicator and we used perceived social disability (the WHODAS 'getting along' domain) and loneliness (the de Jong-Gierveld loneliness questionnaire) as our affective indicators of social dysfunction. Using these separate scores we calculated a social dysfunction composite score. The analyses cautiously linked greater social dysfunction among MDD patients to diminished DMN connectivity, specifically within the rostromedial prefrontal cortex and posterior superior frontal gyrus. These effects were most prominent when high and low social dysfunctioning MDD groups were compared, with the dimensional effects being more subtle. Of note, the effects emerged only as a function of the *integrated social dysfunction composite*, with no independent effects being observed for the affective and behavioral social indices when examined separately.



**Figure 2:** graphic overview of part II in this thesis in which we studied the role of the Default Mode network in social dys-function in MDD, SZ and AD

**Chapter 5** elaborates on the work presented in Chapter 4. We explored DMN integrity as a function of social dysfunction among SZ (N=48) and AD (N=47) patients, as well as age-matched healthy controls (HC; N=55). Social dysfunction was operationalized using the SFS as behavioral indicator of social dysfunction and

loneliness as an affective indicator. Our analyses interestingly showed that affective and behavioral indicators of social dysfunction are independently associated with diminished DMN connectional integrity, specifically within rostromedial prefrontal subterritories of the DMN. The combined average effect of these indicators on diminished DMN connectivity was even more pronounced (both spatially and statistically), comprising large sections of rostromedial and dorsomedial prefrontal cortex.

Together, the findings in chapters 4 & 5 largely support the widely acknowledged role the DMN apparently plays in social dysfunction.

INTEGRATION OF MAIN FINDINGS

Is social dysfunction a transdiagnostic trait in neuropsychiatric disorders?

In chapters 2 and 3, we described affective and behavioral indicators of social dysfunction for MDD, SZ and AD. We used this pragmatic approach to describe differences in social dysfunction based on the assumption that the neurobiological underpinnings of the subjective, affective evaluation of social interactions (i.e. loneliness, self-perceived social disability) are thought to differ from those underlying the more objective, behavioral aspects of social interactions (i.e. frequency of participating in social activities).<sup>8-10</sup> Examining social dysfunction as a transdiagnostic trait is a novel approach. Few transdiagnostic questionnaires exist to describe multifactorial aspects. Affective and behavioral indicators of social dysfunction have provided a way to promote a more detailed understanding of social dysfunction. Table 1 describes the effect sizes for MDD, comorbid anxiety and MDD, SZ and AD patients as compared to corresponding healthy control groups for behavioral and affective indicators of social dysfunction. As only a few questionnaires overlapped in our analyses of MDD, comorbid anxiety, MDD (NESDA data) and SZ/AD (PRISM data), we were unable to directly compare effect sizes for all concepts across the three disease populations. However, for our assessment of loneliness and perceived social disability, we used similar instruments.

Behavioral indicators of social dysfunction across 3 neuropsychiatric conditions

Our findings indicate that, on a behavioral level MDD, SZ and AD patients are largely impaired (see Table 1). Behavioral impairment seems strongest among SZ patients, followed by AD patients and lastly by the MDD patients. However, a direct comparison remains difficult due to the differing samples and methods used

to assess social functioning in MDD versus SZ/AD patients. The social activities questionnaire for example contains questions on frequency of five social activities (such as cultural events, trips to nature or amusement park etc.) scored on a 6-point Likert scale, while the Social Functioning Scale is an extensive questionnaire that contains 7 subscales (e.g., pro-social activities, withdrawal, perceived independence/competence) with most questions scored on a 3-point Likert scale. In terms of statistics, one might argue that the social activities questionnaire has a relatively higher specificity (lower scores are likely to indicate fewer social activities), but a lower sensitivity (impairments in social functioning are likely to remain undiscovered). The Social Functioning Scale, on the other hand, has a reversed profile with high sensitivity (is likely to pick up any social dysfunction) but low specificity (e.g., the subscale ‘perceived independence’ might be different in AD patients because of practical reasons). In light of these differing profiles, it may be the case that social dysfunction is slightly under-reported in the MDD patient group, and slightly over-reported in the SZ and AD groups. When comparing healthy controls to MDD and co-morbid anxiety/MDD patients, the effect sizes for social support are smaller than those of other behavioral indicators of social dysfunction. This may indicate that these patients feel almost as supported as healthy controls, although given current literature this seems unlikely.<sup>21</sup> It is also possible that our social support proxy, the Close Person Inventory, was less sensitive than instruments used in other studies.

Affective indicators of social dysfunction

How patients perceive social dysfunction can be rather different. The de Jong-Gierveld loneliness questionnaire was used for all groups making a direct comparison between the groups possible.<sup>22</sup> The perceived social disability (WHODAS) questionnaire we used was nearly identical in all groups. One question regarding sexual activity was replaced by a question about participation in community events, making the perceived social disability score from the NESDA sample slightly different from the PRISM sample.<sup>6</sup> Our findings indicate that MDD and SZ patients feel lonelier and experience a higher level of disability in social functioning than do AD patients. Moreover, AD patients do not seem to feel more lonely or socially more disabled than their healthy control peers. MDD and SZ patients experience similar levels of loneliness, as the effect sizes – when comparing their scores to controls – are quite similar (see Table 1, effect sizes ranging from 1.1 to 1.5). Interestingly, the rater-perceived social disability of AD patients was much higher as compared to the self-rated perceived social disability in AD patients (see Table 1). This suggests that AD patients do experience problems in affective social functioning (similar as for the behavioral indicators of social dysfunction), but do not themselves report this as markedly ‘impaired’ social functioning. For MDD and SZ feelings of loneliness

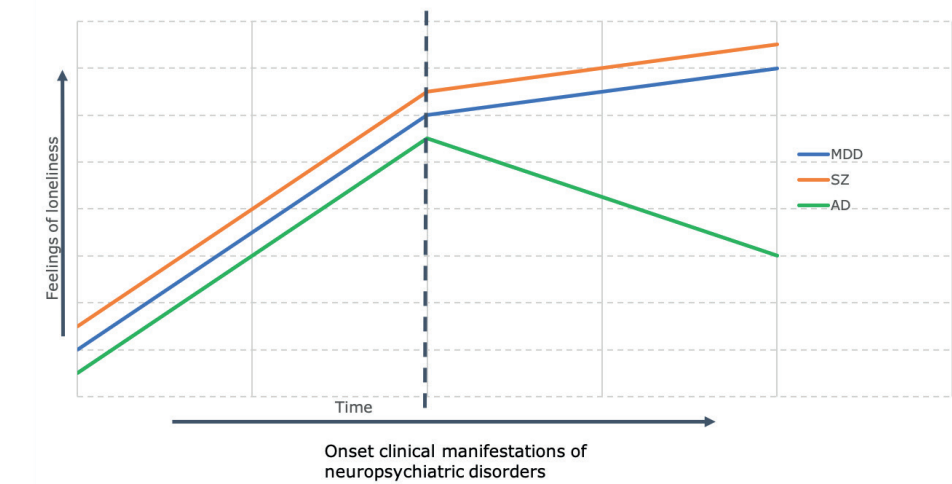
have been described consistently in many different studies.<sup>13–16</sup> The important role of loneliness in the increased likelihood for AD has also been described relatively consistently.<sup>17–19</sup> In these studies, *feeling* lonely was more important than objectively being socially isolated for the development of AD-like symptoms. However, loneliness was not related to AD pathological findings.<sup>18,19</sup> It has been suggested that due to AD pathology, a loss of awareness gives patients an overly positive view of their own social functioning, possibly leading to underreporting of their impairments.<sup>20</sup>

Table 1: Effect sizes for MDD, comorbid anxiety and MDD, SZ and AD patients as compared to corresponding healthy control groups for behavioral and affective indicators of social dysfunction

|                                             | MDD<br>(N=393) | Comorbid<br>anxiety/MDD<br>(N=748) | SZ<br>(N=56) | AD<br>(N=50) |
|---------------------------------------------|----------------|------------------------------------|--------------|--------------|
| Behavioral indicators of social dysfunction |                |                                    |              |              |
| Social network size                         | 0.5            | 0.8                                | na           | na           |
| Social activities                           | 0.5            | 0.8                                | na           | na           |
| Social Support                              | 0.2            | 0.4                                | na           | na           |
| Social Functioning Scale                    | na             | na                                 | 1.8          | 1.1          |
| Affective indicators of social dysfunction  |                |                                    |              |              |
| Loneliness                                  | 1.1            | 1.5                                | 1.5          | 0.1          |
| Affiliation                                 | 0.3            | 0.4                                | na           | na           |
| Perceived social disability                 | 1.2            | 1.8                                | 1.4          | 0.2          |
| Rater perceived social disability           | na             | na                                 | 1.7          | 1.3          |

An additional possible explanation comes from the ‘adaptive predisposition’ theory, whereby loneliness is supposed to be the main driver to engage in social contact, with the aim of mitigating potential adverse outcomes of social isolation.<sup>10,21–24</sup> In other words, loneliness may serve as an adaptational state to create a shift in social balance as a consequence of the neuropsychiatric disorders, and as such, functions as driver to social engagement. Following this theory, loneliness could occur at a higher level in MDD, SZ and AD during a prodromal phase, with continued intensified feelings of loneliness in MDD and SZ happening after the clinical manifestation of the neuropsychiatric disorder (see Figure 3). This notion is further supported by longitudinal research on loneliness in MDD patients.<sup>25</sup> In the adaptive predisposition theory, loneliness acts as motivational drive to engage in social interactions as a way to prevent worse prognostic outcomes in MDD and SZ. For AD, loneliness levels tend to develop fairly similarly to those of MDD/SZ during the prodromal phase. However,

subsequent to the full clinical manifestations of the disorder feelings of loneliness decrease, possibly due to a 'point of no return'. When this 'point of no return' is reached, the AD has progressed too far and the body is no longer able to adapt to the social homeostasis and therefore the social homeostasis set-point is lowered. This theory builds upon existing literature on loneliness as a risk factor for MDD, SZ, and AD.<sup>15,17,19,26,27</sup> However, the question remains: which came first, the chicken or the egg, i.e. the neuropsychiatric disorders or the changed socioaffective state? With the largely cross-sectional, observational studies described in this thesis we are unable to provide a definitive causal pathway. However, in the NESDA analyses described above, we established that perceived social disability among patients is predictive of still having a depressive and/or anxiety diagnosis as much as two years later. Of course, the chicken and the egg both exist. There is evidence for both directions. It is quite possible that a vicious cycle develops in which poor social functioning and mental health impinge one another in a downwards spiral of illness.



**Figure 3:** schematic illustration of theoretical 'adaptive predis-position' of affective states, here operationalized as loneliness. MDD, SZ and AD patients experience feelings of loneliness in a prodromal phase based on previous research. MDD and SZ patients continue to experience intense feelings of loneliness after the onset of clinical manifestations of the disorder. In contrast to AD patients whom experience decreased levels of loneliness.

**Association of mood with social dysfunction**

In both the NESDA and PRISM analyses, we examined the association of mood with social dysfunction. Our data shows that mood and social dysfunction are strongly associated. Across diagnostic groups (MDD/SZ/AD) less favorable mood states are

associated with less favorable social functioning outcomes (i.e. more feelings of loneliness, less social activities). This association was found for both the behavioral and affective aspects of social dysfunction. In fact, the severity of depression and anxiety symptoms were more important determinants of social dysfunction outcomes than disorder severity (e.g. positive/negative symptom severity in SZ, cognitive impairment in AD). It is important to mention that within SZ and AD patients, a clinical diagnosis of current, severe depressive disorder was an exclusion criterion (as assessed by MINI-screen). Excluding severely depressed SZ or AD participants from the PRISM study was done to limit secondary sources of social dysfunction. Within MDD cases, severity of depression was more important as determinant of social dysfunction than the duration of depressive symptoms or age of onset. This strong association between mood state and social dysfunction has been consistently described especially in patients with depression.<sup>28-30</sup>

A possible explanation for these findings could be the so-called hypervigilance in disturbed social functioning.<sup>10,16,22,25</sup> It has been suggested that loneliness or perceived isolation increases vigilance for threat, with more negative social interactions and better memory of negative social information subsequently driving a heightened state of anxiety, stress and depression.<sup>16</sup> In addition, more symptoms of depression could also impact the subsequent social functioning. Quite possibly, the link is bidirectional having mutually reinforcing mechanisms.<sup>31</sup> Within this bidirectional hypothesis, the neuropsychiatric distress leads to a decrease in social activities, which in turn increases feelings of social disability, further aggravating psychological distress.

**Is social dysfunction a transdiagnostic trait across neuropsychiatric disorders?**

Based on the findings presented in this thesis both behavioral and affective aspects of social dysfunction can function as a transdiagnostic trait in neuropsychiatric disorders such as MDD, SZ and AD. Findings show that the behavioral aspects of social function are largely impaired in all clinical groups as compared to healthy controls. Findings also indicate impairments in affective aspects of social function, although in AD this is only reported by external raters not by patients themselves.

IS THERE A NEUROBIOLOGICAL SUBSTRATE FOR SOCIAL DYSFUNCTION ACROSS NEUROPSYCHIATRIC DISORDERS?

Decreased connectivity of the DMN associated with social dysfunction

In chapters 4 and 5, we examined the role of the DMN in social dysfunction among MDD, SZ and AD patients. We found that across these clinical nosologies more social dysfunction correlates with diminished DMN connectional integrity, specifically within the rostromedial prefrontal cortex (rmPFC) subsection of the DMN. The findings from the NESDA and PRISM studies combined suggest that social dysfunction is transdiagnostically associated with DMN integrity, adding to previous findings on DMN centrality to (mal)adaptive human social behavior.<sup>32-39</sup> In addition to the findings in this thesis, more pronounced social dysfunction in relation to DMN dysconnectivity has also been described in other (neuro)psychiatric disorders, though crucially not in a transdiagnostic manner.<sup>40,41</sup>

While not entirely surprising that the rmPFC subsection of DMN emerged as primary effect site in our analyses. Considering the existing literature on the relevance to of the rmPFC to social processes, the robustness of these findings across samples and disorders is noteworthy <sup>32,33,37,40-42</sup>. The rmPFC, as part of the DMN, consistently comes forward in this thesis as effect site with decreased connectional integrity, as a function of increased social dysfunction. The rmPFC is a key node in the core DMN system in addition to the posterior cingulate cortex and the angular gyrus (see figure 4). The core DMN network is believed to primarily facilitate self-referential, personal processes along with parallel subsystem coupling.<sup>35,43</sup> Widespread alterations in the DMN core network function are thus likely to cause widespread disruptions in other DMN subsystems as well.<sup>35,43</sup> This could explain the additional DMN effect sites we documented as a function of social dysfunctioning, including the pSFG in MDD patients, and dmPFC in SZ and AD patients.

Interestingly, both the pSFG and dmPFC are considered to be part of the dorsomedial DMN subsystem, suggesting that disruptions in the core DMN might lead to subsequent disturbances in this subsystem. The dorsomedial DMN seems to support higher-order social processes, such as theory of mind (ToM), mentalizing and social reasoning. Taking this one step further, one may thus assume that adverse connectional changes of the dorsomedial DMN subsystem as documented here could reflect progressive impairments in these higher social functions, as commonly seen in these MDD/SZ/AD.<sup>29,44-48</sup> The cross-sectional nature of the studies presented in this thesis does not allow for causal inferences, yet, preliminary empirical data tends

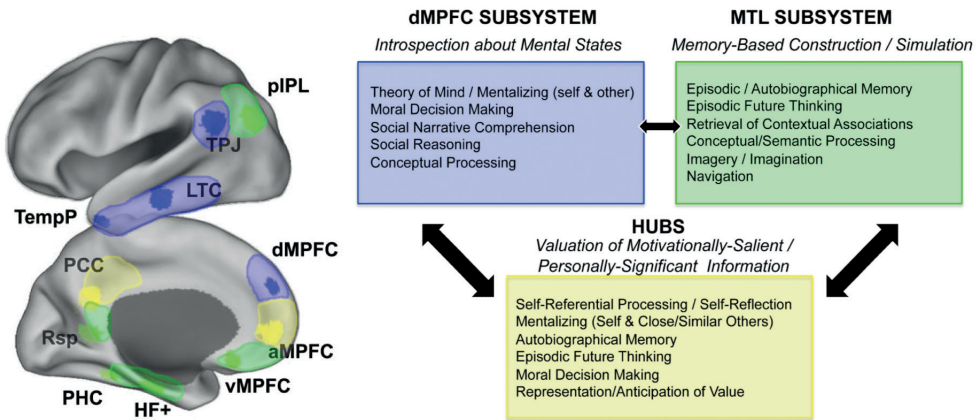
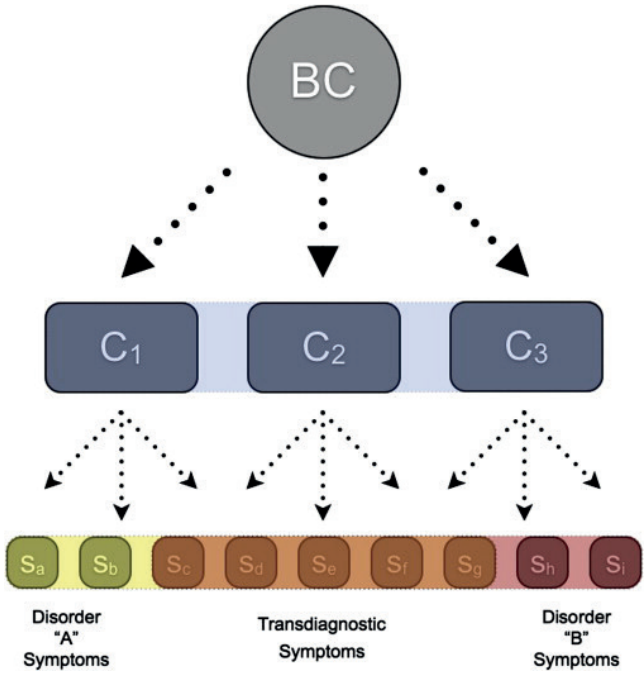


Figure 4: DMN neurobiological system. Left panel: a schematic indication of the DMN with the core hubs (in yellow) with the anterior medial prefrontal cortex (aMPFC), posterior cingulate cortex (PCC). The medial temporal (MTL subsystem) in green include the retrosplenial cortex (Rsp), the parahippocampal cortex (PHC), hippocampal formation (HF+), anterior and ventromedial prefrontal cortex (aMPFC and vMPFC respectively) and the posterior inferior parietal lobule (pIPL). The dorsomedial subsystem (dMPFC subsystem) in blue include temporo-parietal junction (TPJ), lateral temporal cortex (LTC), temporal pole (TempP) and the dorsal medial prefrontal cortex (dMPFC). Right panel: schematic illustration of the suggested functions of the components and tasks that activated the components. Arrows indicate approximate strength of connectivity between the components. (Adapted from Andrews-Hanna, Smallwood, & Spreng, 2014, Ann N Y Acad Sci.)

to suggest DMN dysconnectivity may trigger suboptimal social functioning. For example, rTMS and psychotropic medication manage to normalize DMN functional integrity, and subsequently improve social functioning.<sup>49-52</sup> Furthermore, pre-clinical data shows that experimental manipulation of core DMN subregions or circuits seem to promote positive social behavior in rodents.<sup>23,53,54</sup> Pinpointing the rmPFC as ‘main’ effect site of the DMN dysconnectivity that may bring about social dysfunction would therefore be too short-sighted. In the studies described in this thesis a brain-network approach to social dysfunction was adopted, and the rmPFC is simply a key node amongst the many nodes the DMN system entails. Moreover, one should realize that, in addition to the DMN, other large-scale networks (e.g., Salience, Frontoparietal, Basal Ganglia) may also play a role in human social behavior, and future studies should aim to test this empirically. The DMN, however, is strongly associated with both social dysfunction and psychopathology, more robustly than any other network. The central role of the DMN in social behavior is further illustrated in a recent study on loneliness within the UK biobank, which included a staggering 38701 participants.<sup>32,33,39,55,56</sup>

From a broader perspective, these findings support the hypotheses that neuropsychiatric disorders can be addressed as disorders of brain circuits.<sup>57</sup> With the rise of biological psychiatry, it was previously assumed that psychiatric disorders could be pinpointed to brain lesions, as is possible in some neurological disorders.<sup>58</sup> However, a growing body of literature supports the idea that a single brain lesion cannot explain MDD, SZ, or AD neuropathology despite enormous datasets.<sup>59</sup> Although the “dysconnectivity theory” has a long history that stretches back over a century, recent evidence underscores that disbalances in system-level brain circuits could explain brain-behavior impairments in neuropsychiatric disorders.<sup>10,57,58,60</sup> In other words, our brains have great adaptive power, with precisely choreographed interactions between and within brain circuits, such as the DMN. These brain circuits govern several cognitive processes including social functioning. Dysfunctions of cognitive processes can presumably lead to a wide variety of symptoms within, for example, the social domain. Symptoms are therefore dimensional and continuous.



**Figure 5: Overview of system-level brain circuit dysfunction.** A risk factor for disorder 'A' symptoms and disorder 'B' symptoms alters the function of the brain circuit (BC). This brain circuit governs multiple cognitive processes (C1-C3). Deficits in the domain of cognition leads to dimensions of symptoms (Sa-Si). Part of these symptoms correspond to 'disorder specific' phenomena (Sa and Sb in yellow for disorder 'A'; Sh-Si in red for disorder 'B') but the majority of symptoms will overlap in the two diagnostic categories (Sc-Sg in orange) which corresponds with psychopathology that is dimensional and continuous. (Adapted from Buckholtz and Meyer-Lindenberg, 2012, Neuron)

There are several unifying neurocognitive theories concerning psychopathology, including the “general psychopathology factor”, “common symptoms/circuits model of psychopathology”, and the “dysconnectivity theory”. While important differences exist between them, there is one common denominator: similar symptoms in different disorders could be explained by similar brain circuit disruptions (see figure 5, as adapted from <sup>58, 57,58,60,61</sup>). In this regard, the DMN can be seen as one of the core functional brain networks that are sensitive to a variety of biological/psychological/ environmental changes that may upset a connectional balance. As a disbalance in one core network quite possibly leads to disruptions in other networks, a disbalance in one DMN subsystem likely leads to disruptions in the other subsystems of the DMN.<sup>35,43,62,63</sup> It may be that DMN dysconnectivity, irrespective of its origin, could induce core deficits in circuits specifically governing social processes, ultimately leading to transdiagnostic symptoms such as social dysfunction.

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## Is there a neurobiological substrate for social dysfunction across neuropsychiatric disorders?

Decreased DMN connectional integrity, specifically within the rostromedial prefrontal subterritory of the DMN, seems associated with higher levels of social dysfunction (affective and behavioral), across MDD, SZ and AD patients. These findings suggest that DMN connectional changes might be a transdiagnostic feature of social dysfunction.

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## STRENGTHS & LIMITATIONS

To the best of our knowledge, we are the first to investigate social dysfunction as a transdiagnostic trait in a diverse set of neuropsychiatric disorders (MDD, SZ and AD), and additionally examine social dysfunction as a pejorative factor for DMN integrity across these disorders. We used distinct neuropsychiatric disorders to limit confounding in the transdiagnostic approach of social dysfunction. Examined clinically, genetically or pathophysiologically overlapping neuropsychiatric disorders would provide less information on social dysfunction as a possible transdiagnostic trait. Additionally, we used an integrated approach by using both affective and behavioral indicators of social dysfunction. To date, most studies have been limited to one nosology with one disease specific instrument, making a direct comparison difficult at best. This is further illustrated by the lack of transdiagnostic

instruments to assess social dysfunction in neuropsychiatric disorders, also covered by our study examining possible social dysfunction paradigms.<sup>6</sup> We extend the current literature with this transdiagnostic approach to capturing a notoriously difficult to define concept like social dysfunction, across three distinctively different neuropsychiatric disorders. In addition, we took this transdiagnostic theory one step further, by examining the association of DMN integrity and social dysfunction across these disorders. However, these strengths are – as always – accompanied by limitations.

*Cross-sectional design* - All studies conducted were primarily cross-sectional in nature and observational in design, thereby not allowing for causal inferences. In addition, the sample sizes differed among clinical groups and (especially for the SZ and AD patient groups), were relatively small. Longitudinal research in preferably larger samples is warranted to tackle this limitation. Fortunately, it came as great news that the PRISM project has been funded with another EU-grant to continue this line of research. The upcoming PRISM 2 projects, will include new data collections to increase the sample sizes for investigation, and it now will – beyond AD and SZ – also include MDD as a third patient population.

*Multi-dimensional assessment of social dysfunction* - We isolated affective and behavioral aspects of social dysfunction. This approach was largely motivated by findings suggesting that subjective experiences of social functioning are different from the more objective measurements.<sup>8–10</sup> However, they remain a vast oversimplification of a notoriously complex phenomenon. Building on previous research, affective and behavioral indicators of social dysfunction seem to capture differences adequately when there are many questionnaires available. A limitation in this thesis is that not all questionnaires used are identical in the clinical groups. Especially the comparison between MDD and SZ/AD patients on a behavioral aspect of social dysfunction remains difficult. Although in a clinical sample the approach isolating affective and behavioral aspects of social dysfunction is pragmatic, in an imaging sample it was difficult to uphold this split because of limited sample sizes and power. Whether isolating behavioral and affective aspects of social dysfunction should be maintained in future research is debatable. On one hand; differences emerged when using a more refined approach isolating behavioral and affective aspects. One aspect of social functioning could be impaired, whilst the other is not (i.e. one could feel lonely although levels of social behavior are normal as is illustrated in chapter 2), they do not correlate perfectly. On the other hand, the question is whether this division is necessary to gain more insight into the underlying neurobiology of social dysfunction. We used an integrated composite score of social dysfunction, including a behavioral and affective measure, for the DMN integrity

analyses which showed connectional disturbances. Also, difficulties in maintaining a behavioral and affective distinction, arise for example when patients are biased by their disease state (i.e. AD patients do not perceive themselves as lonely, possibly because of underreporting as is described in chapter 3). Gaining more insight into the potential added value of isolating behavioral and affective aspects of social functioning is an important issue for future research.

*Self-report nature of social dysfunction assessments* - All used instruments are reliable and validated for the clinical groups studied. However, a limitation is the measurement of social dysfunction by self-report questionnaires. Social processes are hard, if not impossible, to capture and reduce to scores on a questionnaire. Who can reliably discriminate in the answer, differences between 'sometimes', 'every now and then', 'several times' or 'on occasion'? For the affective and more evaluative aspects of social dysfunction, the most reliable option is to ask an individual how they *feel* about the social contacts they engage in. This could be extended by the use of ecological momentary assessment, for example, making the assessment less dependent on the spur of the moment.<sup>64</sup> For behavioral indicators, the more objective measurements of social dysfunction, passive sensing would be a useful addition to this type of research. Passive sensing, through the use of smartphones for example, could employ passively following social explorations or communications of the participants the way that the BEHAPP application innovatively does (described more extensively below).<sup>65,66</sup> Another, important addition to self-report instruments, is the involvement of significant others for a thorough examination of social dysfunction. Participants may have an overly positive or negative view of their own social functioning.<sup>67</sup> A significant other could provide more insight in to (longterm) social processes and social dysfunction.

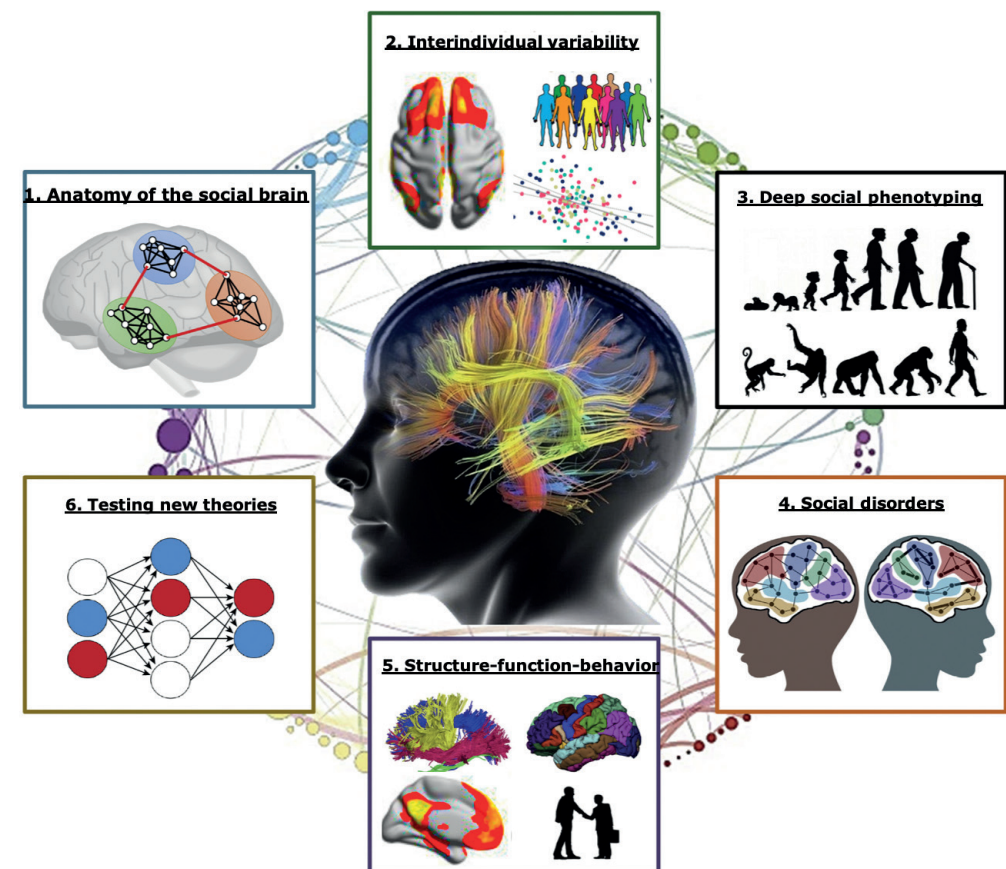
*Brain correlates of complex human behaviors* – Our knowledge about how our brain works when we lie in an MRI scanner is increasing. Over the years more consensus exist on how to correct for multiple comparisons or to improve test-retest reliability. However, there are still limitations to the neuroimaging field. Brain correlates of complex human behaviors suffer from replicability problems mainly due to the wide variety in analyses, techniques and pipelines. Moreover, the current heterogenous data collection methodology in the field that only worsens these replicability problems. To remedy this, we standardized inclusion, data collection and study protocols across participating sites to minimize such limitations. However, our findings need to be further confirmed in larger study samples, although the recent findings on DMN-social dysfunction relations in the UK Biobank seem encouraging (58). Fortunately, the upcoming PRISM 2 will allow for further replication and extension of our findings.

## RECOMMENDATIONS FOR FUTURE DIRECTIONS

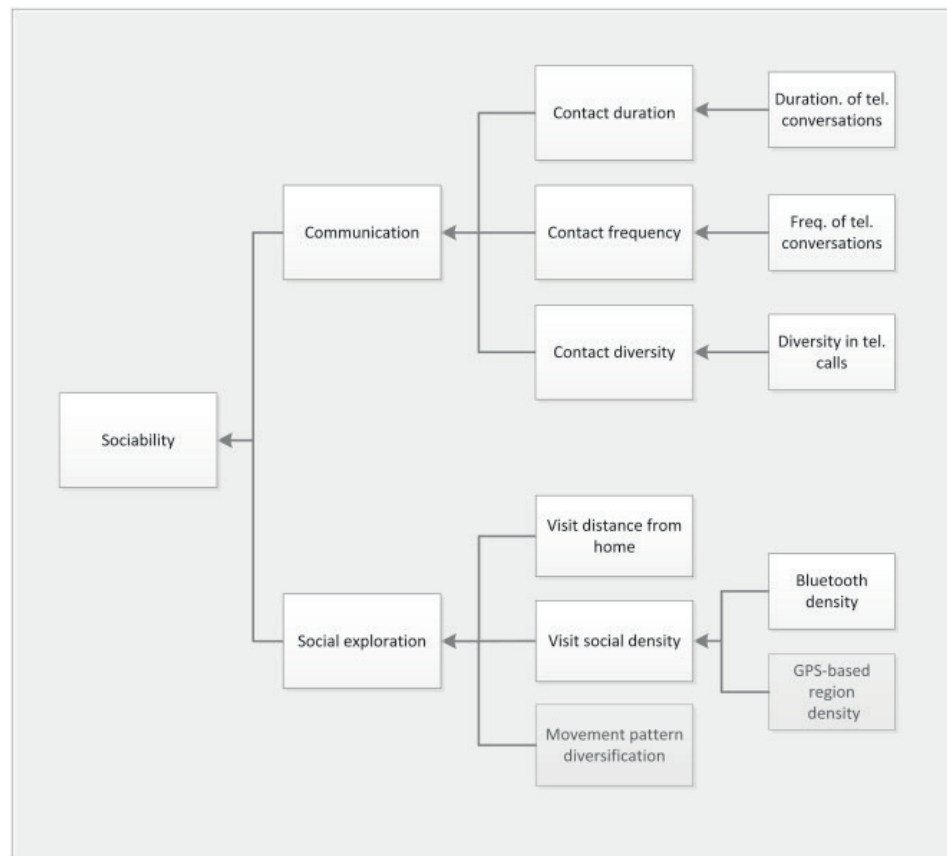
As proposed by the RDoC criteria, future research should aim to combine multilevel data to progress our understanding of complex phenomena like social dysfunction. (see figure 6, as adapted from <sup>68</sup>). However, this requires a fundamental change in how research is commonly performed. Fortunately, recently more emphasis has been placed on the integration of information by both multidisciplinary and interdisciplinary teams to create the best landscape for tackling complex system problems (i.e., human behavior & neuropsychiatry). This includes complex methods to combine multiple systems such as genetics, molecular structures, cytoarchitecture, connectivity, behavior and ultimately mental disorders.<sup>68–70</sup>

An interesting novel tool to add to the multilevel data integration in future years could be the employment of smartphone-based data. From an ocean of data that can be collected from the smartphone, currently it is unknown which aspects are best used as digital biomarkers of social activities and behavior. For example, it is not necessarily the content of what has been written but rather subtle differences in the latency between space and letter or the time between scroll and click that have been shown to correlate nicely to cognitive and affective states, although samples are small and do not include clinical groups.<sup>71</sup> Identifying *the* most promising digital biomarker is a challenge well illustrated by a thermometer analogy as described in 2018 by Chauvain and Insel.<sup>72</sup> Although the relevance of body warmth to fever was known already by the ancient Greeks, and thermometers were available as early as in the 17<sup>th</sup>/18<sup>th</sup> centuries, the thermometer omitted in clinical care due to a lack of standards. Only in the late 19<sup>th</sup> century a psychiatrist collected over 100.000 observations to define a normal or abnormal body temperature.<sup>73,74</sup> This analogy illustrates that we not only need to find the right ‘temperature-measuring scale’, we also need to validate this digital biomarker in large samples across different groups. Indeed, many more questions are still open for debate, such as the privacy puzzle and data ownership. Raising questions such as: who owns the data but also who’s responsibility is it to act upon an altered ‘digital biomarker’? In the realm of social functioning quite a few novel digital developments have been made. For example the BEHAPP smartphone application is an innovative application that can be installed on an Android phone to passively monitor social interactions (i.e. frequency and diversity of calls, time spent on social apps such as WhatsApp) and social density of visited locations (i.e. visiting Bluetooth dense areas, diversity in visited locations) with an integrated sociability score (see figure 7, as adapted from <sup>65</sup>).<sup>65,66</sup> To date, preliminary results from the use of the BEHAPP application in the PRISM study are promising and the validity of an unbiased, data-driven digital measure demonstrated. However, the numbers in our sample were small, and that

is why we could not include this data in our analyses as yet. Low numbers were partly due to refusal (especially among SZ patients this was a factor, possibly due to paranoid psychotic beliefs.<sup>66</sup>) In addition, using the iOs system did not allow the data extraction needed for the BEHAPP. These practical and feasibility issues require more attention and solutions for future studies.



**Figure 6: Schematic illustration for several levels of integrative data in the transdiagnostic domain of social functioning (described in a clockwise manner).** 1. A large body of evidence is already available on the anatomy of the social brain, which could be even further integrated with connective, functional data in humans and animals. 2. Examine interindividual variability of functional connectivity and social behavior in transdiagnostic samples. 3. Deep social phenotyping to fully grasp the commonalities and differences in social behavior and affect. 4. Examine social disorders such as prosopagnosia, autism and other disorders with distinct lesions as examples for discontinuity. 5. Collecting multimodal brain data with functional and diffusion imaging, combined into structure – function-behavior information. 6. Testing new theories guided by new neurobiologically realistic models for social functioning. (Adapted from Wang and Olson, 2014, Trends Cogn Sci.)



**Figure 7: overview of measurements integrated in the BEHAPP sociability score** with two main pillars: communi-cation and social exploration (adapted from (Eskes et al., 2016, Transl. Psychiatry)

Other results with this smartphone application suggested discrepancies between self-reported versus observed social functioning in SZ and AD patients parallel to the observed discrepancies in self-report versus rater-observed perceived social disability of SZ and AD patients described in this thesis.<sup>75</sup>

Until the promising digital biomarker is widely available, there is one rather simple, pragmatic approach that could significantly improve transdiagnostic research into social (dys)functioning; the availability of a transdiagnostic self-report instrument on social dysfunction. One of the limitations is the lack of generalizability of some of the used questionnaires. Most questionnaires are developed specifically for a disorder with disorder specific questions. Future research needs to take this simple, yet crucial, aspect into account. A general questionnaire on social (dys)function would ideally have several domains; 1. behavioral aspects of social functioning

(how often do you go to...), 2. affective aspects of social functioning (how do you experience social contact?), 3. external rating of the behavioral aspects by other person who knows participants and, in the future, 4. objective data from passive sensing, such as through the use of a smartphone application. Its subdomains should have a similar scoring system (for example Likert scale 1-6) which similar maximum outcomes and preferably a normal distribution. Last but not least, it has to be validated in large samples with multiple disorders. This rather obvious development provides researchers the tools for basic assessment of social dysfunction in different disorders to further grasp the differences and commonalities.

## POTENTIAL IMPLICATIONS FOR CLINICAL PRACTICE

### Treatment specifically for the dimensional domain of social dysfunction?

Currently there are no transdiagnostic treatments for social dysfunction. Approaches are primarily disorder specific, such as interpersonal psychotherapy, cognitive behavioral therapy (CBT) and psychoeducation for MDD patients, facial emotion perception and mentalizing training for SZ patients and social projects in AD patients.<sup>28,46</sup> Broadly, interventions can be divided into four categories according to the literature on loneliness<sup>76</sup>: I) *changing cognitions*, II) *social skills training and psychoeducation*, III), *supported socialization or have a 'socially-focused supporter'*, IV) *wider community approaches*. Changing cognitions focusses on how people think about their social relationships. Targeted training, such as conversational ability, are part of the social skills training. Supported socialization entails a guided way towards novel activities or groups. Wider community approaches include interventions with groups that appeal to a wider range of members. Currently, none of the mentioned interventions are robustly evidence based.<sup>76</sup> Biological approaches such as a psychopharmaceutical intervention (i.e. methylphenidate, oxytocin, allopregnanolone or similar medications) have also been suggested, but few are used in every day clinical practice as a transdiagnostic medicine.<sup>28,77–80</sup>

Although more research is needed to uncover novel treatment options for social dysfunction, a study describing helpful treatments already available for various disorders might be a more pragmatic approach. Patient organizations increasingly lobby for more treatments aimed at quality of life improvement, rather than merely symptom-reduction. According to patients and care-givers, social dysfunction is one of the most debilitating symptoms in neuropsychiatric disorders.<sup>20,81</sup> However, improvement of social dysfunction is still often a side-effect of treatment but not a treatment goal in itself. Unfortunately, recovery or stabilization of a

neuropsychiatric disease is often not parallel to recovery of social dysfunction.<sup>31</sup> This is partly illustrated by the residual of social functioning impairments in patients *recovered* from anxiety and depressive disorders as described in this thesis. Various disorder-specific treatments with modules aimed at improving social dysfunction already implemented in daily practice, could be further explored as transdiagnostic treatment options. For example, a combination of CBT (used for MDD patients), mentalizing training (used for SZ patients) and widely available methylphenidate (prescribed for AD patients suffering apathy) may be most effective for the majority of patients suffering from social dysfunction. In short, there are a great many improvements we can make for millions of patients suffering from social dysfunction in MDD, SZ and AD. Sadly, treatments focused on social functioning are generally lacking.

Finally, transdiagnostic treatment principles include universally applied therapeutic principles such as shared-decision making and a good therapeutic alliance.<sup>82</sup> In daily practice this could involve asking your patients in which (social) domain they feel comfortable or need help with. Importantly, you can ask if they would appreciate any help.

## TO CONCLUDE

Based on the findings presented in this thesis both behavioral and affective aspects of social dysfunction seem to be a transdiagnostic trait in neuropsychiatric disorders such as MDD, SZ and AD. The findings show that the behavioral aspects of social dysfunction are largely impaired in all the clinical groups as compared to the healthy controls. The findings also indicate impairments in affective aspects of social dysfunction, when all data is combined including the rater perceived social disability. Decreased Default Mode Network (DMN) connectional integrity, specifically within its rostromedial prefrontal sub-territory, seems associated with higher levels of social dysfunction (affective and behavioral) across MDD, SZ and AD patients. These findings suggest that DMN connectional changes could be a transdiagnostic neurobiological manifestation of clinical social dysfunction. The work described in this thesis contributes to the body of evidence on social dysfunction in neuropsychiatric disorders, underscoring the relevance of deep phenotyping social behavior and neurobiological substrates underlying this phenomenon. Future research should focus on transdiagnostic assessment of social dysfunction that integrates neuro-bio-psychosocial levels of information.

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## Addendum

A

## ABOUT THE AUTHOR

Ilja Maria Josephien Saris was born in Deventer, the Netherlands on the 9<sup>th</sup> of April 1987. After graduating from her secondary school Etty Hillesum Lyceum 2005) in Deventer in 2005, she moved to Maastricht to start with the bachelor Psychology at Maastricht University. After a year she started Medical School and combined it with bachelor Psychology. Starting in the national rowing competition, she decided to quit bachelor Psychology and focus on Medical School. In 2012 she moved to Amsterdam for her last year of Medical School and started a scientific internship at VUmc studying gender dysphoric adolescents, where her interest in scientific research was sparked. After obtaining her medical degree in 2012, she started working at GGZ inGeest in an outpatient clinic for anxiety and depressive disorders. In April 2014 she started her specialist training to become a psychiatrist at GGZ inGeest. Since her interest in carrying out scientific research was still present, she pursued a scientific career combining it with her psychiatry residency. In April 2016, Ilja started her PhD at prof.dr. Penninx group on social dysfunction as a transdiagnostic phenomenon. During the first two years of her PhD she focused on data-collection for the PRISM study and analyses from the ongoing NESDA study. In 2018 she returned to psychiatry residency at the Zaans Medisch Centrum and was trained as a Mentalization Based Treatment (MBT) therapist and group therapist. For her final PhD year in 2019/2020 she focused on analyses from the PRISM study.

Currently she is in her last months of vocational training psychiatry residency and working at the emergency psychiatry department, at GGZ inGeest.

Ilja lives with her husband Roland in Amsterdam, together with their son Olav (2017) and daughter Pia (2021).



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Pippi langkous

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## *"Shelter from the storm"*

Bob Dylan

Lieve Roland; jij houdt niet van kleffe romantiek (zeker niet als die op papier staan en gedeeld wordt met anderen) maar dat is even vette pech; je bent samen met een eeuwige romanticus en liefhebber van clichés. Hier komt ie dan:

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## *"You ain't a beauty but hey you're alright"*

Bruce Springsteen

Lieve, knappe, grappige Olav, kleine dondersteen van me, & mooie, lieve, slimme, nieuwsgierige Pia, door jullie zijn alle kleuren in de regenboog helderder en mooier.

## *"You ain't alone"*

Alabama Shakes

Ilja

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