Neuroscience and Biobehavioral Reviews 164 (2024) 105839

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Default mode network dynamics: An integrated neurocircuitry perspective on social dysfunction in human brain disorders

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ARTICLE INFO

Keywords:
Behaviour
Adaptive social functioning
Brain communication
Neuropsychiatric spectrum
Transdiagnostic

ABSTRACT

Our intricate social brain is implicated in a range of brain disorders, where social dysfunction emerges as a common neuropsychiatric feature cutting across diagnostic boundaries. Understanding the neurocircuitry underlying social dysfunction and exploring avenues for its restoration could present a transformative and transdiagnostic approach to overcoming therapeutic challenges in these disorders. The brain's default mode network (DMN) plays a crucial role in social functioning and is implicated in various neuropsychiatric conditions. By thoroughly examining the current understanding of DMN functionality, we propose that the DMN integrates diverse social processes, and disruptions in brain communication at regional and network levels due to disease hinder the seamless integration of these social functionalities. Consequently, this leads to an altered balance between self-referential and attentional processes, alongside a compromised ability to adapt to social contexts and anticipate future social interactions. Looking ahead, we explore how adopting an integrated neurocircuitry perspective on social dysfunction could pave the way for innovative therapeutic approaches to address brain disorders.

1. Introduction

The world we inhabit is a complex web of social interactions, and as a social species, we heavily depend on the processing of social information to navigate through it. Due to the evolutionary pressure related to social environments, the human brain has evolved with a significant specialisation in processing social stimuli (Dunbar and Shultz, 2007; Dunbar, 2009). This specialisation spans from neurotransmitter regulation to neural network functioning, giving rise to what is commonly referred to as the "social brain" (Dunbar, 2009). The quality and quantity of our social interactions profoundly impact our overall well-being and health, extending this influence on other species as well (Ike et al., 2020). Naturally, social isolation, a consequence of limited social interaction, emerges as a critical factor elevating the risk of mortality and health issues, even surpassing the well-known risks of smoking and excessive alcohol use (Cacioppo and Hawkley, 2009; Eisenberger and Cole, 2012; Holt-Lunstad et al., 2010).

The notion that our complex social environments played a pivotal role in shaping human evolution has gained popularity, underscoring the development of intricate neural networks associated with social behaviour (Dunbar and Shultz, 2007; Dunbar, 2009; Porcelli et al., 2019). Recent research highlights the importance of brain-body interactions in this context, suggesting that physiological processes and neural mechanisms collectively influence the development and functioning of the social brain (Goyal et al., 2015; Sherwin et al., 2019). These interactions provide a more comprehensive understanding of how the social brain has evolved and operates, emphasising the integrative nature of brain and bodily processes in shaping social cognition and behaviour.

Paradoxically, the very complexity and sophistication of our social brain may contribute to its vulnerability to neuropsychiatric disorders (Burns, 2004; van den Heuvel et al., 2019). A variety of major neuropsychiatric disorders manifests impairments in the social brain (Kas et al., 2019; Porcelli et al., 2019). Neuropsychiatric disorders are prevalent, multi-factorial conditions accompanied by several alterations to neural function (Grande et al., 2016; Kupfer et al., 2012; Lord et al., 2018; Mueser and McGurk, 2004). Beyond genetic and symptomatic overlaps (Ardesch et al., 2023), these disorders share a pronounced behavioural phenotype marked by social deficits, suggesting a common neurobiological foundation for social dysfunction outside traditional diagnostic categories (Cotter et al., 2018; Kas et al., 2019; Porcelli et al., 2019). Recognising this common neural basis presents an opportunity to

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https://doi.org/10.1016/j.neubiorev.2024.105839
Received 14 May 2024; Received in revised form 25 July 2024; Accepted 31 July 2024
Available online 2 August 2024

advance treatments and research methodologies, emphasising patient stratification and adopting a more holistic approach to neuropsychiatric research (Kas et al., 2019; Lanooij et al., 2023).

Here, we focus on the brain networks that underlie the various aspects of social behaviour. The brain's Default Mode Network (DMN) emerges as a neurobiological system involved in shaping our complex social phenotype (Andrews-Hanna et al., 2014; Buckner et al., 2008; Mars et al., 2012a; Saris et al., 2022; Saris et al., 2020) and recent studies have implicated alterations to the DMN in various neuropsychiatric disorders (Brown et al., 2018; Dillen et al., 2017; Lee et al., 2020; Mars et al., 2012a; Simic et al., 2014), sparking the hypothesis that the DMN might play a key role in social dysfunction in these conditions and offering a way out of a current stagnation in treatment development (Kas et al., 2019).

This Perspective posits the DMN as a central player in the neurocircuitry underlying social behaviour and its aberrant forms. We explore social dysfunction across the spectrum of neuropsychiatric disorders, stressing why uncovering its shared neurocircuitry is crucial. Furthermore, we delve into the robust association between social functions and both intra- and internetwork dynamics within the context of brain disorders. We offer an integrated forward-looking neurocircuitry perspective, showcasing the DMN's potential to reshape therapeutic approaches for social dysfunction in neuropsychiatric patients. Furthermore, our framework offers valuable direction for refining the diagnostic system concerning brain disorders.

2. The DMN anchors in the social brain

Around three decades ago, researchers pinpointed the initial key components of our brain involved in social behaviour, including the orbitofrontal cortex (OFC), amygdala, and temporal cortex (Brothers, 1990). Soon after, additional regions such as the medial prefrontal cortex (mPFC), the hypothalamus, the striatum, the hippocampus, and the anterior cingulate cortex (ACC) were added to this centre of the social brain (Porcelli et al., 2019). Ideally, the interplay among these foundational components enables us to effectively detect and process social stimuli from our environment. Upon perception, there is a delicate balance between regions crucial for affiliation and aversion, along with the collaborative function of our mirroring and mentalising networks, which govern proper behavioural responses (Bickart et al., 2014a; Porcelli et al., 2019).

Social functioning is a fundamental aspect not only for humans but also for a diverse range of species across various taxa, including amoeba (Gregor et al., 2010), drosophila (Ramdya et al., 2017), mice (Kondrakiewicz et al., 2019) and primates (Kudo and Dunbar, 2001). The brains of these organisms exhibit complex systems related to social behaviour, with an increasing degree of similarity to human social systems corresponding to the social complexity of the organism (Challis and Berton, 2015; O'Connell and Hofmann, 2011; Wilson and Koenig, 2014). The evolutionary conservation of these networks underscores the importance of their study in enhancing our understanding of social functioning.

Notably, several of the brain areas involved in social behaviour, including the ACC, precuneus, and mPFC, extensively overlap with the DMN (Ma and Zhang, 2021) (Fig. 1). The DMN stands out as one of the few large-scale networks identified in humans, but also subsequently recognised across a range of other socially complex mammalian species investigated to date (Garin et al., 2022; Hayden et al., 2009; Hsu et al., 2016). It is often referred to as a task-negative intrinsic system specialised in internal processes such as future planning, reminiscing, and daydreaming (Yeshurun et al., 2021), in which, generally speaking, decreased activity is associated with cognitively demanding external tasks (e.g., a complex mathematical exercise) and increased activity with introspective activities (e.g., self-reflection) (Raichle et al., 2001). The system is thus active by default. Yet, a reversed relationship between DMN activity and task performance is not always obvious. Certain nodes within the DMN demonstrate activity throughout cognitive processing, suggesting a more intricate and dynamic role in cognition (Mars et al., 2012a; Weber et al., 2022). As described by Yeshurun and colleagues (2021), the DMN truly is 'the meeting point of the idiosyncratic self and the shared social world'. This large-scale brain network is involved in an array of social functions (Mars et al., 2012a; Meyer, 2019; Schilbach et al., 2008), ranging from self-referential processes (Qin and Northoff, 2011) to empathy (Spreng et al., 2009; Yeshurun et al., 2021). The DMN anchors in the social brain and alterations to this network might play a pivotal role in the manifestation of neuropsychiatric symptoms.

Indeed, changes in DMN functionality have been linked to various brain pathologies (Mohan et al., 2016). Schizophrenia (SZ), a significant neuropsychiatric disorder characterised by impaired social functioning and altered DMN activity and connectivity (Ardesch et al., 2023; Bilderbeck et al., 2019; Saris et al., 2022), exhibits structural and white

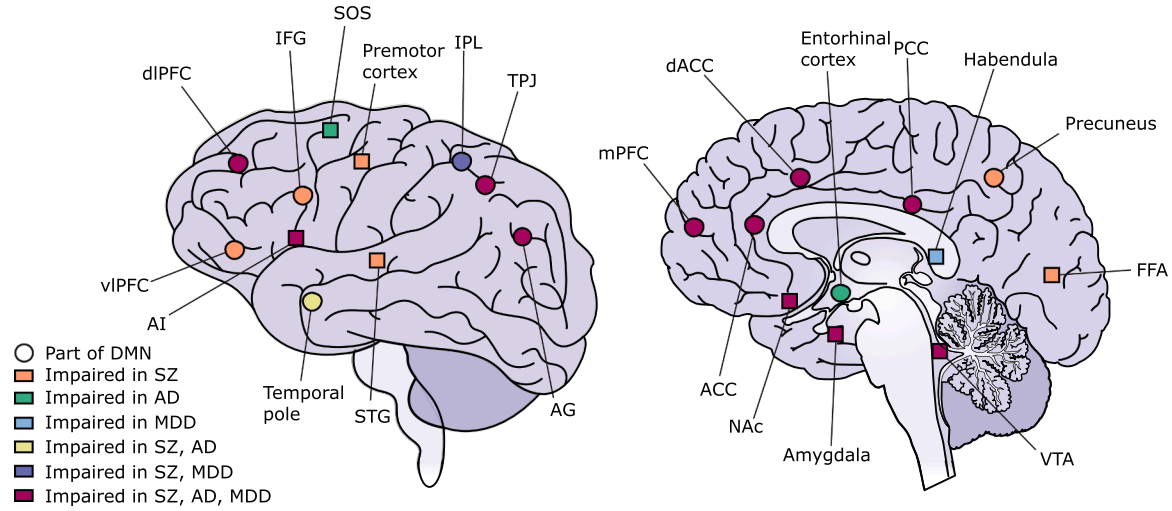

Fig. 1. Overlapping regions of the DMN and the social brain affected in SZ, AD, and MDD. Several regions of the social brain overlap with the DMN (circles) and are affected by major neuropsychiatric conditions. Figure based on (Porcelli et al., 2019) and (Green et al., 2015). SZ = schizophrenia; AD = Alzheimer's disease; MDD = major depression disorder; DMN = default mode network; FFA = fusiform face area; STG = Superior temporal gyrus; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; ACC = anterior cingulate cortex; TPJ = temporoparietal junction; PFC = prefrontal cortex; VTA = ventral tegmental area; NAc = nucleus accumbens; SOS = superior orbital sulcus.

matter irregularities in key regions of the social brain (Fig. 1), particularly those involved in social cognition (Di et al., 2009; van Erp et al., 2016). For instance, alterations in the PFC's regulating force on the amygdala in SZ lead to impaired emotion control in humans (Green et al., 2015), while mentalising and mirroring abilities are impaired due to decreased regulation of the right inferior parietal lobule and posterior superior temporal gyrus (pSTG), affecting imitation, empathy, and motor resonance (Bickart et al., 2014a; Green et al., 2015). Moreover, decreased activity in core social brain areas such as the ventromedial PFC (vmPFC), OFC, mPFC, and the inferior frontal gyrus in SZ aligns with disturbances in mentalising networks (Green et al., 2015), many of which are considered crucial components of both the social brain and the DMN (Mars et al., 2012b; Porcelli et al., 2019) (Fig. 1). Alterations to the mPFC and amygdala in the context of SZ have been confirmed by animal studies (Esmaeili and Grace, 2013).

Altered DMN functioning and associated social deficits have been implicated in major depressive disorder (MDD). Social dysfunction, a recognised hallmark of MDD, often precedes other symptoms and persists even after recovery from other depressive manifestations (Kupferberg et al., 2016; Rhebergen et al., 2010). Individuals with MDD exhibit impairments in the amygdala, impacting their responses to social cues and naturally leading to changes in social behaviour (Fig. 1). Changes in amygdala responsiveness can profoundly influence social behaviour. For example, variations in the amygdala's reaction to social rejection are directly linked to emotional distress (Neugebauer et al., 2020). Furthermore, difficulties in recognising emotions and a negative bias towards emotional stimuli are common in MDD, possibly arising from impaired top-down regulation of emotional processing, with the dorsolateral PFC (dlPFC) playing a key role (Groenewold et al., 2013). Disruptions in mentalising abilities and reduced empathy observed in MDD are associated with key structures within the DMN (Conson et al., 2015; Cusi et al., 2012; Drevets et al., 2008; Kupferberg et al., 2016; Scalabrini et al., 2020). Moreover, reduced connectivity within the broader DMN has been linked to anhedonia and the severity of negative biases in depression and anxiety (Goldstein-Piekarski et al., 2022).

Alzheimer's disease (AD) represents another significant neurological disorder where both the DMN and social functioning play crucial roles. AD patients exhibit a range of social behavioural symptoms, including apathy, emotional detachment, and social isolation (Saz et al., 2009). In AD patients, there is a notable decline in the brain's ability to engage in mentalising, with advanced-level mentalising capacities initially affected, followed by a gradual deterioration in basic skills (Bora and Berk, 2016). The degree of mentalising disability positively correlates with atrophy levels in areas of the DMN (Bickart et al., 2014b; Bora et al., 2015). Apathy in AD is not only associated with grey matter atrophy in the dlPFC, striatum and ACC (Boublay et al., 2016), but also correlates with white matter damage, particularly impaired connectivity between the ACC, OFC, limbic areas, and the basal ganglia (Theleritis et al., 2014) (Fig. 1). These regions are crucial for the processing of social rewards and the motivation to engage in social interactions, suggesting that disruptions in these areas can lead to a reduction in sociability commonly observed in apathy. These findings underscore the association between social dysfunction and AD, as well as the link between alterations in the DMN and the progression of AD.

Social functioning and the DMN are implicated in autism spectrum disorder (ASD) as well. Although ASD is highly heterogeneous, it is often characterised by social deficits such as aberrant social communication through poor speech development and poor expressive language, lack of social reciprocity, and lack of interest in others' emotions (Barak and Feng, 2016; Bauminger et al., 2003; Lord et al., 2000). These social deficits are strongly related to the brain's ability to process social information relative to oneself and to the emotions and intentions of others (Padmanabhan et al., 2017). Predictably, ASD patients exhibit a range of DMN aberrations. For instance, studies of self-referential processing indicate reduced activation in the PCC and mPFC in ASD patients (Kennedy and Courchesne, 2008), as well as decreased connectivity between these two core DMN regions (Lombardo et al., 2010). Additionally, diffusion tensor imaging studies report white matter abnormalities in ASD. Notably, the white matter tracts along the cingulum bundle, which connect the mPFC and PCC, show decreased fractional anisotropy, a measure of fibre density and myelination, in ASD patients (Catani et al., 2016). Collectively, these studies demonstrate impairment of the DMN as well as social deficits in ASD patients.

Beyond the major disorders addressed earlier, various disorders, such as attention deficit hyperactivity disorder, bipolar disorder (BP), Parkinson's disease, mood and anxiety disorders and epilepsy, exhibit impairments in both social and DMN functioning (Ardesch et al., 2023; Doucet et al., 2020; Goldstein-Piekarski et al., 2022; Mohan et al., 2016). Yet, while a spectrum of conditions demonstrates an association between disruptions in DMN activity and challenges in social functioning, a comprehensive and integrated explanation of this link remains elusive.

3. The DMN as a neurobiological substrate of social behaviour

Early speculation of the functional role of the DMN lacked a concrete large-scale network concept. However, in 1997, Shulman proposed that heightened combined activity of individual DMN nodes during passive conditions might signify ongoing processes such as unconstrained thoughts (Shulman et al., 1997). Another groundbreaking study by Andreasen in 1995 found DMN regions active during spontaneous thinking, suggesting involvement in episodic memory retrieval (Andreasen et al., 1995). Studies showing a positive relationship between the connectivity between the DMN and the hippocampus, and episodic memory retrieval, provide support to this early notion (Huijbers et al., 2011; Murphy et al., 2021).

These early studies hinted at an integrated role of this extensive network in episodic memory formation, inner thought, and anticipation of future events. Novel perspectives emerged through brain imaging studies in psychiatric and neurological disorders, where light was shed on the link between DMN functioning and social behaviour (Buckner et al., 2005; Greicius et al., 2004, 2007; Porcelli et al., 2019; Whitfield-Gabrieli and Ford, 2012). Here, we delineate the DMN's role as a neurobiological substrate of social behaviour, examining it from an integrated regional and network-level standpoint.

3.1. DMN function in the context of stimulus-driven network dynamics

Recent studies extend our understanding of the DMN's role in socio-cognitive and behavioural processing by underscoring its interactions with the task-related frontoparietal network (FPN) and the salience network (SN) (Chao et al., 2023; Menon and Uddin, 2010; Sridharan et al., 2008). Described as the 'triple-network model,' this framework elucidates how the SN facilitates the processing of behaviourally relevant external stimuli, activating the FPN while inhibiting the DMN. This process enhances attention and diminishes self-referential processes. Conversely, in the absence of external stimuli, the SN releases its suppression of the DMN, allowing self-referential processes (Schimmelpfennig et al., 2023). Dynamic cross-network communication, with the SN acting as a 'network switch' operated by environmental demands, seems essential for effectively navigating social environments (Fig. 2).

Inherently, various social deficits and associated mental disorders are linked to impaired switching between task-related and resting-state networks. The SN-mediated switch, involving the anterior insula (AI) and dorsolateral ACC (dlACC), shows overactivity in affective disorders and neuroticism (Massullo et al., 2020; Paulus et al., 2003; Paulus and Stein, 2006; Stein et al., 2007). Low AI involvement is related to depersonalisation and emotional detachment in post-traumatic stress disorder patients (Fenster et al., 2018), and left-right insula hypo-connectivity correlates to symptoms of negative bias, anhedonia and threat dysregulation in patients suffering from mood and anxiety disorders (Goldstein-Piekarski et al., 2022), while clinical phenotypes in mood and anxiety disorders were not associated with circuit or regional

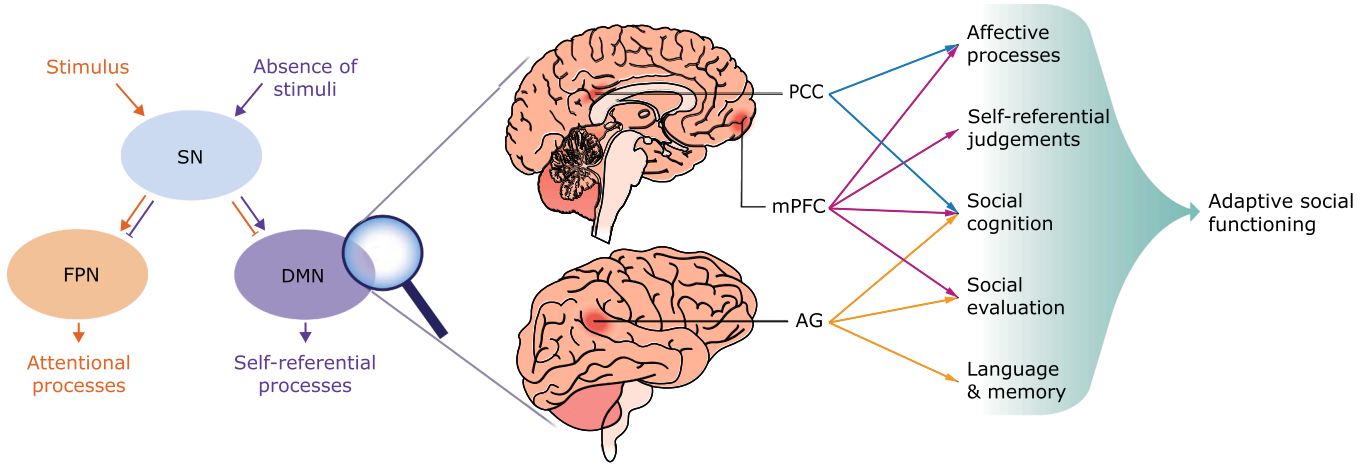

Fig. 2. Illustration of a model depicting the Default Mode Network's (DMN) role in social behaviour. Social stimuli trigger salience network (SN)-mediated suppression of the DMN, and activation of the frontoparietal network (FPN) during attentionally demanding tasks. In the absence of stimuli, this suppression is followed by a DMN activation initiating self-referential processing. SN core regions serve as a switch that shapes the DMN's role in social behaviour (left). Individual key nodes within the DMN, such as the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) and angular gyrus (AG), form an interconnected network with distinct social functions. The DMN acts as an integrative system, combining various social operations to create an ongoing internal narrative, crucial for anticipating future social events and ultimately contributing to adaptive social behaviour (right).

connectivity changes within the FPN (Goldstein-Piekarski et al., 2022). Moreover, reduced functional connectivity (FC) between these networks has been observed in SZ patients (Moran et al., 2013; Orliac et al., 2013; White et al., 2010). ASD patients show lower AI and ACC activity during social tasks (Di Martino et al., 2009), and FC changes correlate with social symptom severity (Uddin et al., 2014). Abnormal FC patterns are also observed in patients with BP and other neuropsychiatric conditions (Sha et al., 2019). These findings highlight that context-dependent network dynamics should not be neglected when examining the DMN's role in social functioning.

3.2. *Individual DMN nodes contribute to overlapping social functions*

A growing body of research affirms the DMN's engagement in social and cognitive functions, highlighting distinct properties of different DMN nodes and their interactions with each other and other brain networks (Wang et al., 2020) (Fig. 2). Therefore, it is relevant to consider the fundamental aspects of DMN functionality through a nodal perspective as well. For instance, the mPFC and PCC are differentially involved in self-other distinctions (Denny et al., 2012; Menon, 2023; Wang et al., 2020), the left angular gyrus (AG) in language-based semantic judgments, and the right AG in social-evaluative functions (Mancuso et al., 2022; Menon, 2023) (Fig. 2). The mPFC is involved in the generation of stimulus-independent thoughts, and the rostro-medial PFC (rmPFC) mainly supports self-relevant socio-cognitive, and socio-affective processes (Andrews-Hanna et al., 2014), but also contributes to constructing future social scenes and regulating emotional responses based on past experiences (Andrews-Hanna et al., 2010; Li et al., 2014). These findings highlight the diverse functions of different DMN nodes in various social cognitive processes, supporting the notion that the DMN contributes to a spectrum of social functions rather than having a singular role.

Several individual DMN regions exhibit aberrant connectivity or activity in patients suffering from a variety of neuropsychiatric disorders, including SZ, BP, and MDD, with the PCC and mPFC being particularly affected (Doucet et al., 2020). For instance, ASD patients show reduced activation of the PCC and mPFC during self-referential processes and self-versus-other distinctions (Kennedy and Courchesne, 2008; Morita et al., 2012), along with diminished connectivity between these nodes (Lombardo et al., 2010). Additional brain imaging studies reveal diminished structural integrity and FC within the DMN of AD patients, aligning with AD-associated atrophy and decreased metabolic rates, and associated with decreased social mentalising abilities (Li et al., 2013; Liu et al., 2014; Zhu et al., 2013). Importantly, Saris and colleagues demonstrated a transdiagnostic correlation between DMN connectional integrity and social dysfunction in MDD patients (2020), and in AD and SZ patients (2022), specifically within the rmPFC. Lastly, when mapping neurocircuits to behavioural symptoms of depression and anxiety, the group of Goldstein-Piekarski showed that lowered connectivity between the AG and anterior mPFC correlates with more severe rumination (Goldstein-Piekarski et al., 2022). These studies underscore that connectional deficits between and within core DMN regions may disrupt crucial behavioural functions essential for social behaviour, and they could be seen as missing building blocks of an integrative system for social functioning.

4. An integrative system for social functioning

Dynamic transitions between three essential networks shape healthy social behaviour. In socially demanding tasks, sensory stimuli activate the FPN and suppress the DMN through the SN, ensuring adaptive responses to social demands. The AI, a core SN region, facilitates seamless shifts between external social processing and intrinsic mental processes (Menon and Uddin, 2010; Sridharan et al., 2008). Hence, dysregulation of the dynamic interplay between the FPN, SN and DMN in neuropsychiatric disorders (Massullo et al., 2020; Moran et al., 2013; Orliac et al., 2013; Paulus and Stein, 2006; Schimmelpfennig et al., 2023; Sha et al., 2019; Stein et al., 2007) may result in aberrant responses to the social environment, inadequate stimulus processing and complications in future social experiences (Fig. 3).

Individual DMN nodes, critical for self-referential judgement, social cognition, and memory, serve as building blocks of social behaviour. Disease-related alterations in nodal connectivity or activity may disrupt the harmonious interplay among DMN nodes, impacting the integration of functions crucial for adaptive social behaviour (Fig. 3). Alterations to the mPFC, central to self-referential judgments and emotional regulation (Denny et al., 2012), seem to play a pivotal role in neuropsychiatric disorders (Saris et al., 2022, 2020), compromising the perception of oneself and others. Such node-specific deficits underscore the nuanced nature of disease-related social dysfunction and the multifaceted nature of the DMN in contributing to effective social functioning.

We propose that, depending on environmental demands, the DMN integrates individual node functionalities, forming a crucial system for constructing and updating an internal narrative of social experiences.

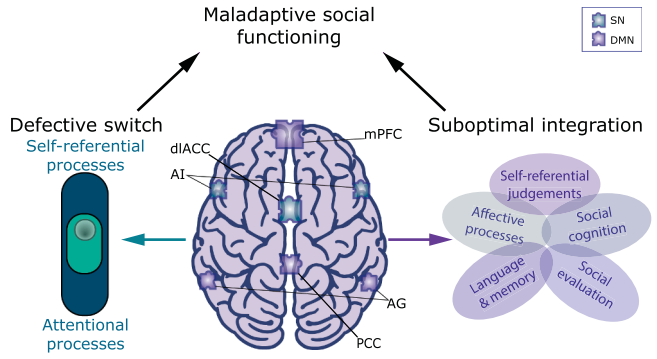

Fig. 3. A simplified framework for neurocircuitry failure and social dysfunction. Dysfunctional DMN regions hinder the optimal integration of distinct social functions, impacting a coherent collection of memories and thoughts crucial for adaptation to ongoing and future social events (right), whereas dysfunctional SN areas act as a faulty switch between self-reference and attention, impeding adaptation to social demands (left). Puzzle piece sizes denote the possible differential level of contribution of deficits in specific areas to social dysfunction. SN = salience network; DMN = default mode network; mPFC = medial prefrontal cortex; dlACC = dorsolateral anterior cingulate cortex; AI = anterior insula; AG = angular gyrus; PCC = posterior cingulate cortex.

This narrative, encompassing memories, self-referential judgments, and contextual information, underlies understanding and navigating social interactions. Disease-related errors in nodal function and a defective switch between attentional and self-referential processes act as missing puzzle pieces, impairing the integration of social information (Fig. 3). Resulting inner narratives lack coherence, contributing to difficulties in responding to future social cues appropriately. The failure of this integrative system causes subsequent maladapted social behaviour (Fig. 3), a key feature across the neuropsychiatric spectrum.

5. Outlook and challenges

Social dysfunction, particularly social withdrawal, represents a common behavioural trait observed across the neuropsychiatric spectrum (Porcelli et al., 2019). Recognising social dysfunction as a transdiagnostic phenotype, rather than a symptom confined to specific psychiatric classifications, has the potential to catalyse progress in treatment development and refine the existing diagnostic framework for brain disorders (Kas et al., 2019). To advance effectively, it is essential to define quantifiable neurobiological substrates underlying social dysfunction, aligning with the rationale of the Research Domain Criteria (RDoC) framework (Insel et al., 2010; Kas et al., 2019).

The DMN's involvement in social (dys)function and various types of neuropathology suggests it is a substrate of the circuitry underlying social behaviour. Therefore, understanding the DMN's precise role in social functioning is critical (Kas et al., 2019). While clinical observations have identified promising associations between changes in intra- and internetwork connectivity and social dysfunction in brain disorders, establishing causality remains challenging. Nonetheless, advancements in both clinical and preclinical research technologies offer innovative pathways to further unravel the neurocircuitry underlying social dysfunction and address questions of causality.

Recent morphometrics and cell-type-specific analyses of MDD-related gene expression correlate structural aberrations to transcriptional changes in MDD patients (Li et al., 2021). Integrating both structural and functional aspects with molecular insights could provide a valuable understanding of the neurobiological basis of social dysfunction as a transdiagnostic disease phenotype. Furthermore, comprehending the impact of disease-related changes in intra- and internetwork connectivity at a cellular level might help identify target pathways amenable to novel therapeutics (Arneson et al., 2018).

Modern advancements in brain mapping, facilitated by deep brain stimulation (DBS), have proven to be powerful tools for integrating functional and structural impairments in various brain disorders. Hollunder and colleagues (2024) recently combined DBS with brain connectomics to map dysfunctional frontal circuits in four distinct brain disorders. Their work demonstrated how dysregulated circuits are functionally linked to clinical manifestations of brain disorders, highlighting DBS's potential in identifying new therapeutic targets for neurosurgery and neuromodulation. Importantly, their work also identified overlaps in the 'dysfunctome' among patients with different brain disorders (Hollunder et al., 2024). Thus, combining neuromodulatory techniques with brain connectomics offers a promising approach to understanding the neurocircuitry underlying social functioning across the neuropsychiatric spectrum.

In another endeavour to map neural circuits linked to behavioural manifestations of brain disorders, Goldstein-Piekarski and fellow researchers (2022) uncovered circuitry aspects associated with transdiagnostic symptoms spanning mood and anxiety disorders. They demonstrated that alterations in connectivity both within and between regions of the default mode and salience networks can predict the intensity of social symptoms, such as diminished pleasure and negative biases (Goldstein-Piekarski et al., 2022). Their findings highlighted the importance of evaluating circuit biotypes for improved patient categorisation and the discovery of new targets for psychiatric interventions.

Advancements in preclinical research facilitate the translation of correlational discoveries from human studies into animal research. For instance, electroencephalography (EEG) can now be employed in freely moving mice and rats, providing equivalent relationships between electrode placements and neuroanatomical substrates. By appropriately scaling for differences in neuronal path lengths, profile responses closely resemble their human counterparts (Kas et al., 2019). Combining wireless EEG with longitudinal assessments of social behaviour in semi-natural settings in rodents (Ike et al., 2023) facilitates the direct translation of human neuroimaging findings and enables the identification of circuits involved in both normal and abnormal social behaviour. The concurrent application of neuromanipulation techniques targeting disease-relevant substrates within these circuits contributes to establishing causality in the link between neurocircuitry and social functioning in the context of brain disorders.

Beyond the challenge of proving a causal relationship between neurocircuitry changes and social deficits, current studies also face the obstacle of discerning the directionality of this link. Several studies suggest that diminished sociability or feelings of loneliness across the lifespan could act as potential precursors to brain disorders, including dementia (Akhter-Khan et al., 2021; Elovainio et al., 2022; Karska et al., 2023). Exploring the effects of manipulating sociability on network dynamics through preclinical investigations would offer valuable insights into the directionality of the relationship between neurocircuitry changes and social deficits in the context of brain disorders. Essentially, it would reveal whether adopting a healthy social lifestyle could serve as a strategy to prevent neuropathology.

6. Concluding remarks

Our perspective sheds light on dysregulated network switching and regional deficits within the context of transdiagnostically disease-related social dysfunction. Approaching social and neurocircuitry deficits as early indicators of brain disorders represents a preliminary step in breaking through the current stagnation in the development of novel therapies. Promising developments in (pre)clinical research present opportunities to tackle existing challenges, fostering a more profound comprehension of the intricate and crucial relationship between social dysfunction and neuropsychiatric disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The application resulting from the PRISM 2 project (www.prism2-project.eu) is funded by the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101034377. This JU receives support from the European Union's Horizon 2020 research and innovation program, EFPIA, and Cohen Veterans Bioscience (CVB). The content of this publication represents solely the views of the authors, and neither IMI JU, EFPIA, CVB, nor the European Commission are liable for any use of the information contained herein.

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