Degree project

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The Default Mode Network's Role in Perceived Social Isolation and Social Connection: A Systematic Review

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Abstract

Feelings of social connection are important to maintain physical and psychological well-being. Perceived social isolation, or loneliness, is the subjective experience of feeling socially isolated and may be a direct threat to our health. During recent years, an increasing amount of people report high levels of loneliness, potentially brought on by the COVID-19 pandemic and its restrictions. Recent research suggests that the brain's default mode network (DMN), a neural network active at wakeful rest, is related to these experiences. This paper aimed to systematically review alterations in the DMN in socially connected and lonely individuals. I searched PubMed and Scopus to find studies using self-report measures of social connection or loneliness, and functional or structural neuroimaging methods on healthy adults. Nine studies were included in this review. Generally, core regions of the DMN typically involved in episodic memory and self-referential processing showed increased activity in lonely individuals and decreased activity in socially connected individuals. These findings may reflect how lonely individuals ruminate about past social events while socially connected individuals attend less to the self. However, methodological heterogeneity between studies limits the conclusions that can be drawn based on these results.

Keywords: default mode network, perceived social isolation, loneliness, social connection

The Default Mode Network's Role in Perceived Social Isolation and Social Connection: A Systematic Review

In my solitude you haunt me
with reveries of days gone by
In my solitude you taunt me
with memories that never die
- Duke Ellington

Social connection is an essential part of human nature. Perceived social connection, or social connectedness, is the subjective experience of being loved, valued, and cared for by others (Eisenberger & Cole, 2012). It can also be described as a positive sense of belonging or feeling linked to others (Bowins, 2021). Having social connections is critical to maintaining psychological and physical well-being (Cacioppo & Patrick, 2008; Diener & Seligman, 2002). Accordingly, lacking social connection threatens our health in numerous ways. High levels of perceived social isolation (PSI; i.e., loneliness) have been associated with depression (Cacioppo et al., 2010), anxiety and suicidal thoughts (Beutel et al., 2017), cardiovascular diseases (Valtorta et al., 2016), poor sleep quality (Cacioppo et al., 2002), cognitive decline (Boss et al., 2015) and premature mortality (Rico-Uribe et al., 2018).

During the COVID-19 pandemic, social distancing, lock-downs, and curfews have become protective measures throughout the globe to contain the spread of the Coronavirus. Consequently, European citizens who report themselves feeling lonely more than half of their time have increased from 12% in 2016 to 25% during the first months of the pandemic (Baarck et al., 2021). Young adults, aged 18-25, were shown to be the most affected group as their subjective ratings of PSI increased from 9% to 35% (Baarck et al., 2021). In a recent study, old adults, aged 68 and above, living in Stockholm, Sweden, reported themselves to have increased psychological burden as a consequence of the first outbreak of the virus (Beridze et al., 2022). Loneliness was reported as the most common stressor, with 33.4% of the participants reporting feeling lonely (Beridze et al., 2022). In the US, a survey from 2020 showed that 36% of approximately 950 respondents felt lonely frequently or most of the time (Weissbourd et al., 2021). Murayama et al. (2021) reported a 6.7% increase in social isolation among Asian populations, and that this increase was also associated with greater loneliness.

PSI is described as the subjective experience of feeling lonely and occurs when there is a conflict between a person's desired level of social connections and actual connections (Baarck et al., 2021). In this regard, PSI differs from objective social isolation in which a person is isolated or alone with few or no social contacts. People may thus feel lonely irrespectively of how many relationships they have if they perceive those relationships to be of poor quality (Baarck et al., 2021; Cacioppo & Hawkley, 2009). Furthermore, PSI predicts changes in behavior, cognition, and physical health that cannot be predicted by objective social isolation alone (Cacioppo & Hawkley, 2009). For example, research shows lonely individuals are less likely to engage in physical activities (Hawkley et al., 2009) and more likely to feel unsafe in their neighborhood (Wen et al., 2006). Loneliness has also been found to be a predictor of changes in IQ, life satisfaction (Gow et al., 2007), depressive symptoms (Cacioppo et al., 2010), and blood pressure (Hawkley et al., 2006). None of these outcomes could be predicted from social network size, suggesting PSI rather than objective social isolation was the predisposing factor (Cacioppo & Hawkley, 2009).

Moreover, people with high levels of PSI show altered cognition in relation to the self and others. For instance, lonely individuals are more likely than nonlonely individuals to expect negative treatment from other people and to perceive others' behavior as threatening (Cacioppo & Hawkley, 2005). In turn, this often makes them socially anxious and, paradoxically, less likely to seek comfort in others (Cacioppo & Hawkley, 2005). When remembering previous experiences of social rejection, or imagining exclusion in the future, lonely individuals make negatively biased and less accurate predictions (Teneva & Lemay, 2020). Furthermore, lonely individuals tend to be more engaged in mental simulations such as nostalgic reminiscences (Wildschut et al., 2006) and ruminating thoughts (Preece et al., 2021). These mental projections of oneself into the past or future have been associated with activity in the default mode network (DMN), a neural network known to be active at wakeful rest (Buckner & Carroll, 2007). This has led to a growing interest in the DMN when investigating the neural mechanisms behind the subjective experience of social connection and PSI (Courtney & Meyer, 2020; Spreng et al., 2020).

The Default Mode Network

One hypothesis is that the DMN's involvement in PSI reflects lonely individuals' greater need for simulating internal representations of social events in the absence of real experiences (Spreng et al., 2020). The DMN is a network known to activate when individuals shift focus from the external to the internal environment and are left undisturbed to engage in spontaneous thinking (Buckner et al., 2008; Buckner & Carroll, 2007; Raichle, 2015; Raichle et al., 2001). Core regions of the DMN include the medial prefrontal cortex, the posterior cingulate cortex, the inferior parietal lobe, and the temporoparietal junction (Buckner et al., 2008; Li et al., 2014; Raichle, 2015). Additional regions sometimes included in the DMN are the hippocampal formation, the lateral temporal cortex, the parahippocampal cortex, the temporal pole, the precuneus, and the retrosplenial cortex (Buckner et al., 2008; Li et al., 2014).

The DMN is involved in various internally focused cognitive skills. For instance, the network is well-known to be involved in spontaneous cognition, or mind-wandering, as well as constructing mental scenes of places or events (Andrews-Hanna et al., 2010; Spreng et al., 2020). Further, the DMN is involved in self-referential memory, processing, and self-projection i.e., thinking about one's past or future (Buckner & Carroll, 2007). Moreover, activity in the DMN has been linked to understanding and inferring other people's actions, intentions, beliefs, and emotions as well as making moral judgments about the self and others (Li et al., 2014). Data from psychedelic and meditation research indicates that decreased activity in the DMN (especially in the medial prefrontal cortex and the posterior cingulate cortex) correlates with an increased self-reported dissolution of the self, supporting the DMN's role in the concept of the self (Millière et al., 2018).

Neuroscientific Methods

Studies investigating PSI and social connection use various brain-imaging methods to measure structural and functional correlates in the DMN. These methods include structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI; Nakagawa et al., 2015), functional MRI (fMRI; Courtney & Meyer, 2020), and electroencephalography (EEG; Grennan et al., 2021). Voxel-based morphometry (VBM) and fractional anisotropy (FA) can be used to investigate changes in white matter structures using structural MRI and DTI respectively (Nakagawa et al., 2015). VBM detects abnormalities in brain anatomy by comparing grey- and white matter density between groups of individuals (Ashburner & Friston, 2000), while FA is a measure of anisotropic water diffusion, which reflects the orientation of white matter fiber tracts (Chua et al., 2008). Neural activation detected by fMRI is measured by changes in the ratio between oxygenated and deoxygenated blood in the brain. This is called the blood oxygen level-dependent (BOLD) signal (Ogawa et al., 1993). The BOLD signal can either be measured as the brain's response to various tasks in task-based designs or as spontaneous fluctuations in resting-state fMRI (Fox & Raichle, 2007). Functional connectivity (FC) refers to what extent neural activity in spatially distant brain regions correlates with each other over time (Friston, 1994). fMRI data can be analyzed using either whole-brain voxel-wise analysis or by choosing specific regions of interest (ROI:s; Poldrack, 2007). In EEG studies, event-related spectral perturbations (ERSPs) measure event-related changes in amplitude of the EEG frequency spectrum (Makeig, 1993). Taken together, these methods serve as objective measures to detect brain activity or regions associated with PSI and social connection.

Measuring Perceived Social Isolation and Social Connection

Researchers use self-report assessments to measure the experience of PSI and social connection. Currently, there is no standardized measure with accepted cut-off scores indicating to which degree a person feels lonely (Baarck et al., 2021). Instead, various psychometric scales exist that either measure PSI by explicitly mentioning the term 'lonely', or by asking questions related to the respondent's social situation. The latter approach is often preferred in research (Baarck et al., 2021). Common measures include the University of California-Los Angeles (UCLA) Loneliness Scale (Russell et al., 1978), the Loneliness Survey by the National Institute of Health (NIH) Toolbox (Health Measures, 2022), and a modified version of the William's Need-Threat scale (Eisenberger et al., 2007). In studies using large populations, brief single-item psychometric scales are often preferred (Baarck et al., 2021). Single-item measures have shown both reliability and validity when investigating the quality of social relationships (Atroszko et al., 2015).

Studies employ different methods to measure social connection. Some methods include a self-other reflection task (Courtney & Meyer, 2020), a social network survey (Hyon et al., 2020), and a visualization task (Hutcherson et al., 2014).

The Present Study

Although PSI and social connection have been well-studied, their exact neural mechanisms are still not fully understood. Lately, research has begun to investigate the DMN's role in producing these subjective experiences. To my knowledge, no review on this topic has yet been done. Thus, the aim of this paper is to systematically review studies reporting alterations in the DMN, or core regions of the DMN, in socially connected and lonely individuals.

To feel socially connected to other people is critically important to maintain physical and mental health. As mentioned previously, feelings of loneliness threaten our health in numerous ways, and during the global Covid-19 pandemic, the amount of people reporting high levels of PSI has increased. It is therefore important to further our knowledge on how the subjective experiences of feeling socially connected, or disconnected, are produced. By understanding the neural mechanisms behind these experiences, we might also understand how to better prevent the damaging effects caused by PSI and promote social connection and individual flourishing.

Methods

Search Strategy

The search procedure in this systematic review was done according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA; Moher et al., 2009). The literature search was performed on the 2nd of March using the electronic databases PubMed and Scopus. To find appropriate studies, the following search string was used; ("social connect*" OR "social isolation" OR "social exclusion" OR loneliness OR lonely OR "social disconnect*" OR alienation OR "perceived social isolation" OR "perceived loneliness") AND ("default network" OR "default mode network" OR DMN OR "medial frontoparietal network" OR "default state" OR "resting-state"

OR "medial prefrontal cortex" OR MPFC OR “posterior cingulate cortex” OR PCC OR “inferior parietal lob*” OR IPL OR “temporo-parietal junction” OR TPJ). Although social isolation differs from PSI, it was included in the search so that studies investigating objective social isolation with additional measures of PSI would not be dismissed. All studies were initially examined and selected by title or abstract. Each selected study was then examined in full text for further assessment of eligibility. The search yielded 454 articles on both Scopus and PubMed (for details, see PRISMA flow diagram, figure 1). After duplicates were removed, 265 articles remained and 15 articles were selected for further screening. Nine articles met all inclusion criteria (see below) and were included in this review.

Inclusion and Exclusion Criteria

Only original studies focusing on the DMN, or core regions of the DMN (medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobe, and temporoparietal junction) in relation to PSI or social connection were included in this review. Included studies had to use (1) healthy participants, (2) a subjective measure of PSI or social connection, and (3) an objective measure of brain activity or regions to be included. Further, all studies had to be (4) published in peer-reviewed journals. Studies were excluded if they (1) only provided measures of objective social isolation, (2) focused on participants with any type of physical or mental disorder, or (3) were animal studies.

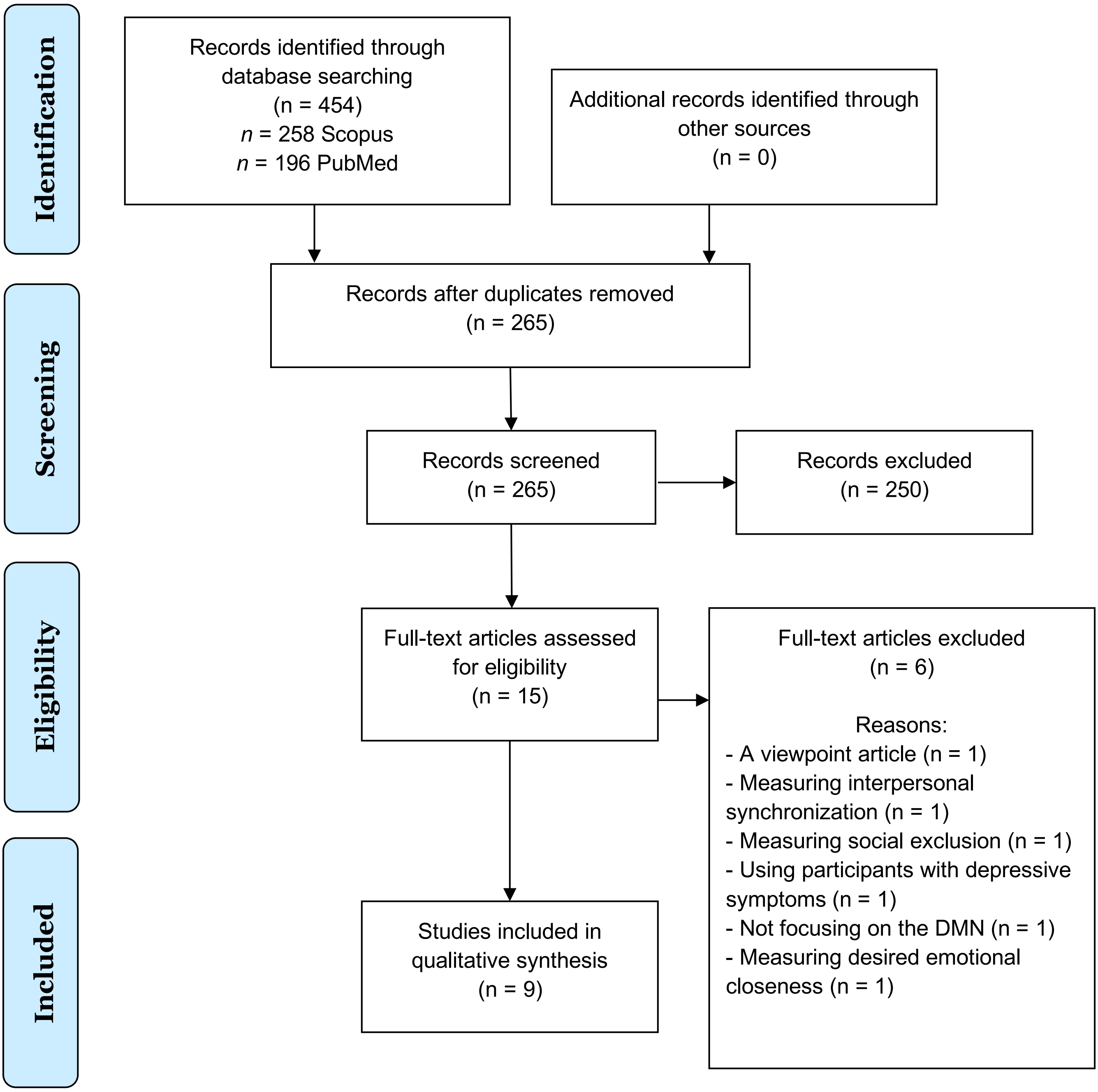
Although symptoms of loneliness and depression are overlapping and often cooccurring, research supports them both statistically and functionally as two separate conditions (Cacioppo et al., 2010). As previously stated, research has shown loneliness as a predictor of depressive symptoms. This review focuses solely on the DMN’s role in producing the subjective experience of loneliness and social connection. The reason to exclude all clinical studies was due to the possible alterations in the DMN that depression or any other type of clinical diagnosis might produce.

Data Extraction

The following data were extracted from each study: sample size, mean age, study design, type of measure used to assess PSI or social connection, type of neuroimaging method, and main outcomes.

Figure 1

PRISMA flow diagram



Note. PRISMA flow diagram, a standard flow diagram used to document the literature search process. Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement." by Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group, 2009, *PLoS Med,* 6(7), p. 3 (doi:10.1371/journal.pmed1000097).

Results

Table 1 summarizes the descriptive statistics of the included studies. Six studies investigated the DMN in relation to PSI (Eisenberger et al., 2007; Grennan et al., 2021; Mwilambwe-Tshilobo et al., 2019; Nakagawa et al., 2015; Spreng et al., 2020; Zajner et al., 2021). Two studies investigated the DMN in relation to social connection (Hutcherson et al., 2014; Hyon et al., 2020), and one study investigated the DMN in relation to both PSI and social connection (Courtney & Meyer, 2020). Taken together, all studies included 40,713 healthy participants. Two studies used the same participant data from the UK Biobank (Spreng et al., 2020; Zajner et al., 2021). These participants were only included once in the calculation of total participants.

Table 1

Descriptive Statistics of Included Studies

Reference per intervention	*N* (included in the analysis)	Mean age (*SD*)	Measures	Neuroimaging method	Study design
Perceived Social Isolation					
Eisenberger et al. (2007)	42 (30)	20.73 (3.23)	N-TWS	TB fMRI, WB	Cross-sectional
Grennan et al. (2021)	152 (147)	40.7 (22.6)	UCLA LS	EEG, ERSP	Cross-sectional
Mwilambwe-Tshilobo et al. (2019)	1200 (942)	28.04 (3.45)	NIH Toolbox	RSFC, fMRI, WB	Cross-sectional
Nakagawa et al. (2015)	776 (776)	20.2 (1.5)	UCLA-LS	MRI, VBM, DTI, FA	Cross-sectional
Spreng et al. (2020)	38701 (38701)	54.9 (7.5)	Single-item, UK Biobank	MRI, WB, DTI, FA, RSFC, fMRI	Cross-sectional
Zajner et al. (2021)	38701 (38701)	55 (7.5)	Single-item, UK Biobank	MRI	Cross-sectional
Social Connection					
Hutcherson et al. (2014)	22 (19)	20.9 (4.1)	Visualization task	TB fMRI, WB, ROI (mPFC)	Cross-sectional
Hyon et al. (2020)	68 (57)	70.66 (6.28)	Social network survey	RSFC, fMRI, WB	Cross-sectional
Perceived Social Isolation and Social Connection					
Courtney & Meyer (2020)	50 (41)	20.2 (4.6)	UCLA-LS, Self-other task	TB fMRI, WB, ROI (mPFC)	Cross-sectional

Note. N-TWS = Need-Threat Williams Scale; UCLA LS = University of California Los Angeles Loneliness Scale; NIH Toolbox = National Institute of Health Toolbox; TB = task-based; WB = whole brain; ERSP = event-related spectral perturbations; RSFC = resting-state functional connectivity; VBM = voxel-based morphometry; FA = fractional anisotropy; ROI = region of interest; mPFC = medial prefrontal cortex.

Functional Alterations in the Default Mode Network

Five studies analyzed brain activity or connectivity in relation to PSI using functional imaging. Of those, one study employed task-based EEG (Grennan et al., 2021), two employed task-based fMRI (Courtney & Meyer, 2020; Eisenberger et al., 2007), and two employed resting-state fMRI (Mwilambwe-Tshilobo et al., 2019; Spreng et al., 2020). Three studies investigated DMN activity in relation to social connection using functional imaging. Of those, two studies employed task-based fMRI (Courtney & Meyer, 2020; Hutcherson et al., 2014) and one study employed resting-state fMRI (Hyon et al., 2020). Table 2 summarizes the main outcomes of all studies employing functional imaging.

Table 2

Results of Included Studies Using Functional Imaging

Reference per intervention	Method	Outcomes
Perceived Social Isolation		
Courtney & Meyer (2020)	TB fMRI	High PSI associated with less similar self-other neural representations in the mPFC and less distinct neural representations in the mPFC and PCC between friends, acquaintances, and celebrities.
Eisenberger et al. (2007)	TB fMRI	Increased activity in the mPFC and left hippocampus associated with high momentary social distress and high end-of-day PSI.
Grennan et al. (2021)	TB EEG	High PSI associated with a slower response while threatening stimuli were present. This reduction in reaction time correlated with left TPJ theta activity. No large-scale DMN activity was detected.
Mwilambwe-Tshilobo et al. (2019)	RS fMRI	PSI associated with greater FC and lower modularity between networks, especially between the DMN and FPN. Low PSI associated with greater FC between the DMN and the LIM network.
Spreng et al. (2020)	RS fMRI	PSI associated with greater within-network FC in the DMN and the VIS network. Greater FC between the DMN and the SOM, DAN, and LIM networks. Decreased FC between the DMN and the VIS network.
Social Connection		
Courtney & Meyer (2020)	TB fMRI	SC associated with more similar neural representations between the self and others in the mPFC and the PCC.
Hutcherson et al. 2014	TB fMRI	SC associated with neural activity in an area extending from the ACC to the dmPFC. Activity in the dmPFC increased during self-directed SC and decreased during other-directed SC.
Hyon et al. (2020)	RS fMRI	SC between individuals was predicted by similar patterns of FC, especially in the DMN.

Note. TB = task-based; fMRI = functional magnetic resonance imaging; PSI = perceived social isolation; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; EEG = electroencephalogram; TPJ = temporoparietal junction = DMN = default mode network; RS = resting-state; FC = functional connectivity; FPN = frontoparietal network; LIM = limbic; VIS = visual; SOM =

somatomotor; DAN = dorsal attention; SC = social connection; ACC = anterior cingulate cortex; dmPFC = dorsal medial prefrontal cortex.

Perceived Social Isolation

Grennan et al. 2021 used an exploratory task-based design to investigate the neural correlates of loneliness and wisdom using EEG. Loneliness was assessed with the UCLA Loneliness Scale, the most commonly used scale designed to measure PSI (Baarck et al., 2021; Russell et al., 1978). The participants estimate on a scale from 1 (*never*) to 4 (*always*) how well statements such as “how often do you feel ‘in tune’ with other people?” or “how often do you feel that you lack companionship?” correspond to their subjective feelings (Russel, 1996). Grennan et al. (2021) found that in relation to an attentional bias task, loneliness was associated with a slower response in the presence of threatening stimuli. ERSP analyses showed that this reduction in processing speed associated with loneliness correlated with increased left transverse temporal theta activity, a region located in the temporoparietal junction (Grennan et al., 2021). Further, the authors reported that no significant relationship was found between loneliness and large-scale DMN activity (Grennan et al., 2021).

Courtney and Meyer (2020) used an exploratory and hypothesis-driven task-based design to assess neural responses associated with self-other closeness and loneliness using fMRI. Loneliness was assessed with the UCLA Loneliness Scale. They found that loneliness mediated the distance between the neural representations of the self and others. Specifically, in a self-other reflection task (for details, see below), lonely individuals showed less similar neural activity patterns between self-representation and other-representation in the medial prefrontal cortex (Courtney & Meyer, 2020). Further, high levels of loneliness were associated with less clear neural distinctions between social categories in the medial prefrontal cortex and the posterior cingulate cortex, such that close friends, acquaintances, and celebrities were more similarly represented to one another (Courtney & Meyer, 2020).

Eisenberger et al. (2007) employed an exploratory task-based design to assess neural activity associated with momentary social distress and end-of-day loneliness using fMRI. A modified 2-item version of the William’s Need-Threat scale was used to assess end-of-day loneliness (Eisenberger et al., 2007; Williams et al., 2000). The participants rated on a scale from 1 (*strongly agree*) to 7 (*strongly disagree*) how well the statements “Today, I generally felt connected to others” and “Today, I generally felt accepted by others” fitted their experience (Eisenberger et al., 2007). Notably, Eisenberger et al. (2007) found that greater activity in the medial prefrontal cortex and the left hippocampus was significantly associated with high levels of momentary social distress and end-of-day loneliness (i.e., PSI). In contrast, greater activity in the anterior cingulate cortex was associated with high levels of momentary social distress during the day but low levels of end-of-day loneliness (Eisenberger et al., 2007).

Mwilambwe-Tshilobo et al. (2019) investigated whole-brain resting-state functional connectivity patterns associated with loneliness and meaning in life using fMRI. Loneliness was assessed using the Loneliness Survey by the NIH Toolbox, a 5-item questionnaire measuring PSI with statements such as “I feel that I am no longer close to anyone” or “I feel lonely” (Health Measures, 2022; Mwilambwe-Tshilobo et al., 2019). The DMN was observed as having a core role in differentiating between loneliness and meaning in life. Loneliness was associated with dense, more extensive between-network functional connectivity, especially in the DMN and the frontoparietal network. Also, low levels of loneliness were associated with greater functional connectivity patterns between the DMN and the limbic network. High levels of loneliness were associated with a less modular intrinsic network organization between brain networks (Mwilambwe-Tshilobo et al., 2019).

Spreng et al. (2020) used an exploratory design to investigate whole-brain resting-state functional connectivity associated with loneliness in large-scale brain networks using fMRI. Neuroimaging and loneliness data was collected from the UK Biobank, a large open-access database with half a million participants (UK Biobank, 2021). To assess loneliness the participants were asked the yes/no, single-item question “Do you often feel lonely?” (Spreng et al., 2020; UK Biobank, 2021). Loneliness was associated with greater within-network functional connectivity in the DMN. Also, in lonely individuals, the DMN showed greater between-network connectivity with other brain networks (somatomotor-, limbic-, and dorsal attention network) than what is typically found in non-lonely individuals. Additionally, loneliness was associated with greater within-network connectivity in the visual network and decreased between-network connectivity between the visual network and the DMN (Spreng et al., 2020).

Social Connection

Courtney and Meyer (2020) used an exploratory and hypothesis-driven task-based design to investigate neural activity patterns associated with self-other closeness using fMRI. Social connection was assessed using a self-other reflection task. In this task, the participants made trait judgments of 16 people from different social categories: the self, 5 provided close others, 5 provided acquaintances, and 5 celebrities. The participants then rated how subjectively close they felt to each person on a scale from 0 (*not at all*) to 100 (*very much*; Courtney & Meyer, 2020). Courtney and Meyer (2020) found that the neural representations of all social categories were organized into three distinct clusters (the self, social network members, and celebrities) in the medial prefrontal cortex. A whole-brain analysis revealed that this neural organization of social targets was also seen in the posterior cingulate cortex and the temporoparietal junction. However, social connection was associated with more similar neural activity patterns between self- and other-representation. Specifically, higher ratings of subjective closeness were associated with greater neural self-other overlap, especially in the medial prefrontal cortex and the posterior cingulate cortex (Courtney & Meyer, 2020).

Hutcherson et al. (2014) used an exploratory task-based design to investigate the neural correlates of social connection using fMRI. Social connection was assessed using a visualization task similar to loving-kindness meditation (Hutcherson et al., 2014; Salzberg, 1995). Each participant completed either the visualization task or a neutral visual imagery task (control condition). During the visualization task, the participants were guided to imagine receiving love from others and directing love towards others while in the fMRI scanner (Hutcherson et al., 2014). Following the scan, all participants rated on a scale from 1 (*not at all*) to 7 (*extremely*) how socially connected they felt during the visualization or the control task. A whole-brain analysis revealed a stronger neural response in an area extending from the anterior cingulate cortex to the dorsomedial prefrontal cortex during the social connection task compared to the control task (Hutcherson et al., 2014). Further ROI analyses showed greater activity in the dorsomedial prefrontal cortex during the self-directed component of the visualization task (receiving love *from* others). Notably, activity in the dorsomedial prefrontal cortex also correlated negatively with the subjective ratings of social connection during the other-directed component (directing love *towards* others; Hutcherson et al., 2014).

Hyon et al. (2020) used fMRI in an exploratory study to investigate if similarities in whole-brain resting-state functional connectivity patterns could predict social connection between individuals. Social connection was assessed using a social network survey. The participants provided the names of the following 7 people; a spouse, up to 5 people they discuss important issues with, and an important person with whom they have infrequent contact (Hyon et al., 2020). The participants were also asked to rank how subjectively close they felt to each person on a scale from 1 (*not very close*) to 4 (*extremely close*; Hyon et al., 2020). Hyon et al. (2020) found that similar patterns of resting-state functional connectivity throughout the brain significantly predicted social connection between individuals. The DMN was the most frequently observed brain network predicting social connection (Hyon et al., 2020).

Structural Alterations in the Default Mode Network

Three studies investigated alterations in grey- and white matter structures related to PSI using structural imaging. Of those, one study employed MRI (Zajner et al., 2021) and two studies used both MRI and DTI (Nakagawa et al., 2015; Spreng et al., 2020). No study employing structural imaging in relation to social connection was identified. Table 3 summarizes the main outcomes of all studies employing structural imaging. One study used both structural and functional imaging and thus appears in both Table 2 and Table 3 (Spreng et al., 2020).

Table 3

Results of Included Studies Using Structural Imaging

Reference per intervention	Method	Outcomes
Perceived Social Isolation		
Nakagawa et al. (2015)	MRI, DTI	PSI was associated with decreased rWMD in the IPL, TPJ, and dmPFC.
Spreng et al. (2020)	MRI, DTI	PSI was associated with increased GM volume in the DMN and greater WM integrity in the fornix.
Zajner et al. (2021)	MRI	Structural deviations associated with PSI were found in the covariance between the hippocampus and the DMN, especially in the CA1, ML, mPFC, PCC, and RSC. These areas were positively associated with WM integrity of the fornix.
Social Connection [a]		

Note. MRI = magnetic resonance imaging; DTI = diffusion tensor imaging; PSI = perceived social isolation; rWMD = regional white matter density; IPL = inferior parietal lobule; TPJ = temporoparietal junction; dmPFC = dorsomedial prefrontal cortex; GM = grey matter; DMN = default mode network; WM = white matter; ML = molecular layer; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; RSC = retrosplenial cortex.

[a] No study employing structural imaging in relation to social connection was found.

Perceived Social Isolation

Zajner et al. 2021 used MRI to assess structural differences in the DMN and hippocampus between lonely and non-lonely individuals. Neuroimaging and loneliness data was collected from the UK Biobank (UK Biobank, 2021; Zajner et al., 2021). To assess loneliness the participants were asked the yes/no, single-item question “Do you often feel lonely?” (UK Biobank, 2021). They found that several structural covariations between the DMN and the hippocampus were divergent in lonely individuals. The most prominent deviations in the DMN were found in the medial prefrontal cortex, posterior cingulate cortex, and the retrosplenial cortex. In the hippocampus, the most prominent deviations were found in the CA1 and molecular layer. Further, these co-existing structural deviations in the DMN and hippocampus seen in lonely individuals were also positively associated with white matter integrity in the fornix (Zajner et al., 2021).

Nakagawa et al. (2015) used an exploratory design to assess whether alterations in white matter structures were associated with loneliness using MRI and DTI. Loneliness was assessed using the UCLA Loneliness Scale. A VBM analysis revealed that loneliness was negatively correlated with regional white matter density in core regions of the DMN. These included the bilateral inferior parietal lobule, the posterior temporoparietal junction, and the dorsomedial prefrontal cortex. No significant result was found between loneliness and white matter structural integrity as measured by FA (Nakagawa et al., 2015).

Spreng et al. (2020) used an exploratory design to investigate both grey- and white matter alterations in large-scale brain networks using MRI and DTI respectively. Neuroimaging and loneliness data was collected from the UK Biobank. To assess loneliness the participants were asked the yes/no, single-item question "Do you often feel lonely?" (UK Biobank, 2021). A whole-brain analysis showed that loneliness was associated with increased grey matter volume in the DMN (Spreng et al., 2020). Further, FA data revealed that lonely individuals had greater white matter integrity in the fornix (Spreng et al., 2020).

Discussion

The aim of this paper was to systematically review studies reporting alterations in the DMN, or core regions of the DMN, in socially connected and lonely healthy adults. A total of nine studies were included in this review for data synthesis. This section includes a summary and a discussion of the main findings reported in the results. Limitations to this review as well as societal and ethical aspects of the included studies will be discussed. This will be followed by some concluding remarks.

The Default Mode Network and Perceived Social Isolation

Seven studies reported functional and structural alterations in the DMN, or core regions of the DMN, associated with PSI. There was great heterogeneity between studies in terms of how PSI was assessed and how each study was conducted. Therefore, it was somewhat unsurprising that several different outcomes were found.

Lonely individuals had increased functional connectivity within the DMN (Spreng et al., 2020) and increased connectivity between the DMN and the frontoparietal- (Mwilambwe-Tshilobo et al., 2019), somatomotor-, dorsal attention-, and limbic networks (Spreng et al., 2020). Further, PSI was associated with increased grey matter volume in the DMN and greater white matter integrity in the fornix (Spreng et al., 2020). The fornix is located in the limbic system and is a major white matter fiber tract connecting the hippocampal system to the medial prefrontal cortex, a core region of the DMN (Spreng et al., 2020; Williams et al., 2020). Previous research suggests that white matter integrity of the pre-commissural fornix is positively correlated with detailed autobiographical memory and imagination of future events (Hodgetts et al., 2017; Williams et al., 2020). The DMN is well-known to be involved in thinking about one's past and future (Andrews-Hanna et al., 2010; Buckner & Carroll, 2007), and lonely individuals are more likely to engage in nostalgic reminiscence and rumination of past events (Preece et al., 2021; Wildschut et al., 2006). Spreng et al. (2020) suggest that the relationship between PSI, the DMN, and the fornix reflects a heightened tendency for lonely individuals to simulate internal, hypothetical social interactions based on memories in the absence of real ones. Interestingly, excessive rumination, characterized by increased DMN activity, has also been seen in depression (Marchetti et al., 2012) which loneliness has been shown to predict (Cacioppo et al., 2010). Further support for this view comes from Zajner et al. (2021) who found structural deviations in the DMN-hippocampus covariation that also correlated positively with fornix integrity in lonely people. However, it should be noted that these two studies used the same data which could potentially limit the conclusions drawn from these findings. Further, Nakagawa et al. (2015) reported no significant association between loneliness and white matter integrity. Instead, they found decreased regional white matter density in core regions of the DMN, suggesting that PSI may alter the myelination and thus slow down the neural transmission within the DMN (Nakagawa et al., 2015). Interestingly, myelin loss has been linked to cognitive decline (Rivera et al., 2021) which lonely individuals seem more likely to be affected by (Boss et al., 2015). Functional connectivity between networks has been observed to reflect the underlying white matter structural connectivity between them (Greicius et al., 2009). It may therefore be contradictory that studies reported PSI to be associated with both decreased white matter density (Nakagawa et al., 2015) and increased within-network functional connectivity in the DMN (Spreng et al., 2020). However, a more recent study investigating the relationship between structural- and functional connectivity within resting-state networks found that they do not necessarily relate to each other (Tsang et al., 2017). More research is needed to understand these findings and how they relate to PSI and the DMN.

Greater PSI was also related to less modular connections between the DMN and other brain networks (Mwilambwe-Tshilobo et al., 2019). Modularity is an indicator of health and refers to how well a network can be divided into smaller, functionally specialized modules with efficient processing (Bullmore & Sporns, 2009; Mwilambwe-Tshilobo et al., 2019; Wig, 2017). Low modularity in brain networks has previously been seen in the aging brain (Rakesh et al., 2020). However, lower global modularity in the brain has also been speculated to benefit episodic memory retrieval (Westphal et al., 2017). Specifically, lower network modularity has, together with greater functional connectivity between the DMN, frontoparietal network, and the hippocampus, been related to more efficient episodic memory retrieval (Westphal et al., 2017). Although speculative, this could mean that lonely individuals have a less modular network organization in the DMN because of their ability to retrieve episodic memories. In turn, this would support the hypothesis by Spreng et al.

(2020), that PSI is associated with the DMN because lonely individuals tend to simulate social interactions based on memories.

In line with this, greater activity in the medial prefrontal cortex and the hippocampus was also found in individuals who showed greater correspondence between momentary social distress during the day and retrospective end-of-day reports of loneliness (Eisenberger et al., 2007). Interestingly, individuals who felt high levels of social distress during the day but reported low levels of loneliness at the end of the day had increased activity in the anterior cingulate cortex, a region typically associated with empathy (Eisenberger et al., 2007; Singer & Lamm, 2009). This suggests that feelings of brief moments of social distress differ from the global valuation of a person's social situation, i.e., how lonely a person feels in general (Eisenberger et al., 2007). Past research has linked both the medial prefrontal cortex and the hippocampus to memory encoding (Brewer et al., 1998; Cabeza et al., 2004), and functional connectivity between these regions correlates with detailed memory descriptions (Yang et al., 2013). The neural activity in those who continued feeling lonely at the end of the day may thus reflect how effectively those memories of social distress during the day were encoded and later retrieved (Eisenberger et al., 2007).

Besides its involvement in memory, the medial prefrontal cortex has been implicated in the concept of the self (Gusnard et al., 2001). This region, together with the posterior cingulate cortex, was shown to keep a structured map of a person's relationships that differed in lonely versus socially connected individuals (Courtney & Meyer, 2020). In lonely people, the neural activity in the medial prefrontal cortex seen while thinking about the self was more distinct from the activity seen while reflecting upon others (Courtney & Meyer, 2020). In contrast, the neural activity associated with others was more similar across social categories. This suggests that loneliness may be associated with an altered neural representation of the self in the DMN, and may explain why lonely individuals perceive themselves as being separated from everyone else (Courtney & Meyer, 2020).

The DMN is important in understanding other people's behavior and mental states (Li et al., 2014), and the temporoparietal junction has especially been involved in this skill referred to as theory of mind (Saxe & Kanwisher, 2003). Greater theta activity in the left temporoparietal junction was observed in lonely individuals while distracted by threatening faces (Grennan et al., 2021). Although the temporoparietal junction is a core region of the DMN, no large-scale activity was found in the network (Grennan et al., 2021). This could be due to the rather limited aim of the study, as PSI was only studied in the context of an emotional bias task (Grennan et al., 2021). Greater theta activity in the temporoparietal junction has previously been linked to stronger implicit intergroup biases (Grennan et al., 2021; Schiller et al., 2019), but with greater significance in the right, rather than the left, hemisphere (Schiller et al., 2019). Still, the findings by Grennan et al. (2021) could potentially reflect lonely individuals' predisposition to expect negative treatment from others as reported by Cacioppo and Hawkley (2005), and warrant further investigations.

The Default Mode Network and Social Connection

Three studies reported functional alterations in the DMN, or core regions of the DMN, associated with social connection. In contrast to loneliness, high levels of social connection were associated with a greater self-other overlap in the medial prefrontal cortex and the posterior cingulate cortex (Courtney & Meyer, 2020). More specifically, when socially connected individuals thought about close others, they activated similar patterns of neural activity as they were while thinking about themselves. The DMN may therefore keep track of our social connections in structured neural maps, and how close we feel to others may be determined by how similar the brain represents those people to ourselves (Courtney & Meyer, 2020). Further, reduced activity in the dorsal medial prefrontal cortex correlated with greater subjective feelings of social connection towards others, while increased activity in the same region correlated with social connection towards the self (Hutcherson et al., 2014). This was taken to suggest that shifting the attention away from internal self-related thoughts may promote feelings of connection towards others (Hutcherson et al., 2014). Interestingly, decreased activity in the medial prefrontal cortex and the posterior cingulate cortex has also been observed in both experienced- and novice meditators during meditation techniques designed to foster social connection and alleviate loneliness (Brewer et al., 2011; Hutcherson et al., 2008; Lindsay et al., 2019). Similar outcomes have been observed in research on classic psychedelics where deactivation of the DMN has been shown to correlate positively with both drug intensity and self-reported dissolution of the sense of self (Carhart-Harris et al., 2012). It has also been suggested that one of the reasons psychedelic substances show promise in therapeutic settings may be because of the increased sense of social connection often reported during psychedelic sessions (Carhart-Harris et al., 2018). However, it is noteworthy that Hutcherson et al. (2014) also found increased activity in the dorsal medial prefrontal cortex when imagining receiving love and care from others. The authors speculate that this may reflect the complexity of generating feelings of social connection, and that it may involve both a shift in attention towards others as well as the ability to extend the self upon others to feel more similar to them (Hutcherson et al., 2014). This would explain the neural self-other overlap seen in socially connected individuals as reported by Courtney and Meyer (2020).

The DMN was also the most significant network that predicted how close individuals were to each other based on their resting-state functional connectivity patterns (Hyon et al., 2020). Another study on adolescent girls has previously failed to find such a relationship (McNabb et al., 2020). However, taken that the DMN goes through developmental changes during the adolescent years (Fan et al., 2021) it could be argued that those similarities in functional connectivity between friends may have developed over time.

Limitations and Future Directions

Several limitations to this review should be considered. Foremost, the heterogeneity between studies makes it difficult to compare the results directly. PSI and social connection were measured either in relation to the brain's intrinsic structure and connectivity or in relation to the neural responses associated with various tasks. Further, different scales were used in assessing PSI. These scales treated loneliness as either a binary or non-binary phenomenon which makes the operationalization of this subjective experience problematic.

Another limitation is that all studies were correlational, meaning the results reported in this review cannot determine a causal relationship between PSI, social connection, and the DMN. It is therefore not possible to know whether the alterations seen in the DMN occur prior to or as a consequence of these feelings. Although some studies used ROI analysis, most studies used a whole-brain approach when analyzing the neuroimaging data. The whole-brain approach is useful to conduct exploratory analyses throughout the brain, but has less statistical power than the ROI method as the number of regions in this approach is more restricted (Madhyastha et al., 2018). Further, all studies used a cross-sectional design which limits the understanding of how these alterations may change over time.

Although the total number of participants in the included studies was quite high, the sample sizes varied between studies. Overall, the studies measuring social connection had the smallest sample sizes which should be taken into consideration when interpreting the results.

Moreover, it should be noted that this review was written by one author only. This increases the risk of potential biases in the search process and the interpretation of the results. Research suggests that more studies may be overlooked if the literature search is conducted by a single reviewer compared to two independent reviewers (Waffenschmidt et al., 2019). There is also a risk that the search string used in this review may have been too limited to find appropriate studies. For example, it may be that studies investigating PSI or social connection in relation to the DMN, but failed to find significant results, were missed. On the other hand, it may also be that such findings are less likely to be published (publication bias) or reported within studies (outcome reporting bias; Moher et al., 2009).

A final limitation is that this review only focused on healthy adults and did not take other covariates such as age, gender, or depressive symptoms into account. Although valuable to the understanding of how the DMN is affected in the healthy brain, it limits the understanding of how the DMN is affected in other population groups. As PSI has been shown to predict depression (Cacioppo et al., 2010), one way forward may be to design longitudinal studies on the association between the DMN and PSI and how it relates to depression.

Future studies are recommended to develop standardized assessment tools to measure PSI and social connection, employ experimental and longitudinal study designs, and have larger sample sizes. Future reviews should also include participants from different age groups and with pathological disorders to get a broader perspective on the relationship between loneliness, social connection, and the DMN.

Societal and Ethical Aspects

All studies included in this review were accepted by ethic committees and collected their data before COVID-19 restrictions. All participants gave their written consent and were screened for clinical diagnoses prior taking part in each study. The increasing amount of people affected by PSI is a worldwide problem. Research on PSI and social connection from a cognitive neuroscience perspective is therefore important, not only for the individual affected by the health-threatening consequences of feeling isolated, but for society at large. Understanding how these subjective experiences relate to structural and functional differences in the brain may forward the knowledge on how to maintain individual health and societal flourishing.

Conclusion

This review aimed to investigate the relationship between the DMN and the subjective experiences of PSI and social connection. Although there was methodological heterogeneity between studies, some interesting findings emerged. Overall, the DMN showed several alterations in regions associated with memory and self-referential mental activity in both lonely and socially connected individuals. Lonely individuals showed greater activity and functional connectivity in the DMN, which could reflect their tendency to ruminate about past events and use their imagination to simulate future social interactions in the absence of real ones. Negative associations with the DMN, such as decreased regional white matter density and network modularity, may also reflect brain deterioration caused by PSI. Decreased activity in the DMN was seen in socially connected individuals, suggesting these feelings are produced by attending less to the self. Although more research is needed, these findings are promising as they help to target interventions designed to alleviate loneliness and promote social connection. Taken together, continued research on the DMN may have a central role in helping to alleviate feelings of loneliness and increasing feelings of social connection.

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