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The emergent relationship between temporoparietal junction and anosognosia in Alzheimer's disease

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Abstract

Anosognosia and impairment of insight are characteristic features of Alzheimer's disease (AD), which can lead to delays in appropriate medical care and significant family discord. The default mode network (DMN), a distributed but highly connected network of brain regions more active during rest than during task, is integrally involved in awareness. DMN dysfunction is common in AD, and disrupted communication between memory-related and self-related DMN networks is associated with anosognosia in AD patients. In addition, the temporoparietal junction (TPJ) is a key region of the "social brain" and also contributes to representations of the self. The exact classification of the TPJ within the DMN is unclear, though connections between the TPJ and DMN have been highlighted in multiple avenues of research. Here we discuss the relationship between the TPJ, DMN, and AD, as well as the potential involvement of the TPJ in anosognosia in AD. We review past and present findings to raise attention to the TPJ, with a specific emphasis on neuroimaging technologies which suggest a pivotal role of the TPJ within large-scale brain networks linked to anosognosia in AD.

KEYWORDS

Alzheimer's disease (AD), anosognosia, default mode network (DMN), temporoparietal Junction (TPJ)

1 | INTRODUCTION

Alzheimer's disease (AD) continues to be the leading cause of dementia, ultimately causing severe global brain dysfunction and necessitating around-the-clock care for patients in late stages (Alzheimer's Association, 2016; Wilson et al., 2012). As a complex neurodegenerative disease, AD causes decreased cognitive and memory capacity, disorientation to time and place, changes in mood and personality, social withdrawal, and other debilitating symptoms (Alzheimer's Association, 2016). Awareness and sensory processing are also significantly impaired in people with Alzheimer's dementia. Clare et al. (2008) describe awareness in this context as a "reasonable perception or appraisal of a given aspect of one's situation, functioning or performance, or of the resulting implications, which may be expressed explicitly or implicitly." While patients with advanced AD generally maintain the capacity for basic sensory-level processing, disparities become evident at more complex and integrated levels of awareness, such as in self-recognition or evaluative judgment (O'Shaughnessy et al., 2021).

Deficits in higher levels of awareness may influence how individuals with AD experience their sense of self due to the diminishing ability to self-maintain (as to "attempt to normalize the situation and minimize difficulties, thus maintaining continuity with prior sense of self") or to self-adjust (as to "attempt to confront the difficulties to adjust one's sense of self accordingly") (Clare, 2003). Incapacity to maintain an accurate sense of self may reflect the impairment known as *anosognosia*. Spalletta et al. (2012) build onto this by suggesting that anosognosia also encompasses "an underestimation of limitations in activities of daily living, failure to use compensatory strategies, and a tendency to adopt dangerous behaviors." Anosognosia is a significant factor in AD, as it is associated with more severe

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cognitive impairment, apathy, agitation, lower adherence to treatments, higher levels of caregiver distress, and other behavioral problems that can cause complications in the care for AD patients (Aalten et al., 2005; Spalletta et al., 2012; Starkstein, 2014; Vogel et al., 2010). Considering the impact of this symptom on quality of life, a better understanding of anosognosia etiology may provide opportunities regarding long-term care and treatment for patients with AD.

The operations of awareness are not isolated to any single brain region, but it is known that the temporoparietal junction (TPJ) plays an essential role in multimodal sensory integration (Karnath & Dieterich, 2006; Matsuhashi et al., 2004), reorienting attention (Bledowski et al., 2004; Corbetta & Shulman, 2002), self-other distinction (Farrer et al., 2003; Ruby & Decety, 2001), self-face recognition (Uddin et al., 2005), visuospatial perspective taking, self-location, and embodiment (Lenggenhager et al., 2006). Not only does the TPJ functionally integrate tactile, proprioceptive, and visual information (Blanke & Arzy, 2005), but it also plays a dynamic role in the default mode network (DMN) (Andrews-Hanna et al., 2010), a distributed but highly connected network of brain regions more active during rest than during tasks.

In an ever-aging population, research investigating global and network dysfunction and related biomarkers is imperative to provide opportunities for novel and early AD interventions. This work aims to explore the potential relationship between anosognosia, the TPJ, and the DMN as it relates to the progression of AD.

Significance

Research into large-scale brain networks utilizing neuroimaging modalities can provide essential insight into Alzheimer's disease (AD) and the debilitating symptoms that manifest with its progression. We suggest an interrelationship of anosognosia as it relates to the progression of AD and to impaired activity within the temporoparietal junction (TPJ) and default mode network. In particular, TPJ activity may serve as an instigator or compensatory mechanism involved in the awareness processes within the AD brain.

2 | THE DMN IN AD

Irregular activity in several large-scale brain networks has been documented in AD patients, one of the most prominent being the DMN, which has been hypothesized by Buckner et al. (2008) to serve as "a specific, anatomically defined brain system preferentially active when individuals are not focused on the external environment." Moreover, research by Andrews-Hanna et al. (2010) has defined the DMN as a large-scale brain network that engages in a multitude of tasks, including social perceptions, contemplating the future, and episodic memory functions. The DMN can be broken down into a midline core and two distinct subsystems: the medial temporal lobe (MTL) subsystem and the dorsal medial prefrontal cortex (dmPFC) subsystem, which includes the TPJ. The same author later proposes that the dmPFC subsystem plays a major role in the introspection and appraisal of our own mental state as well as social information (Andrews-Hanna, 2012).

Various neuroimaging modalities have provided growing evidence regarding the impact of AD on resting-state networks, such as the DMN. A comprehensive analysis of 764 data sets yielded from five AD neuroimaging studies conducted by Buckner et al. (2005) highlighted implications of DMN activity related to developing AD. They proposed that metabolic patterns observed in the DMN in young adults could be indicative of risk for developing AD. A previous work had already suggested that individuals with the apolipoprotein E ε4 allele may exhibit early, reduced hypometabolic patterns (Reiman et al., 1996). They scanned individuals with a familial history of AD with and without the apolipoprotein E ε4 allele, a known genetic risk factor for AD. Their findings reflected a difference among the groups such as those who were presymptomatic and had the apolipoprotein E ε4 allele exhibited significant glucose hypometabolism in prefrontal, temporal, and parietal areas, as well as in regions of the posterior cingulate cortex (PCC), a central node of the DMN. Grothe and Teipel (2016) more recently used data from the Alzheimer's Disease Neuroimaging Initiative database (http://adni.loni.usc.edu/) to extend these findings and showed hypometabolism as well as atrophy and amyloid deposition being ubiquitous throughout the DMN. However, while predominant in the DMN, they also found distinct hypometabolic patterns in limbic and heteromodal association networks as well as within the frontoparietal control network. While further explorations are needed, neuroimaging-based glucose metabolism and AD stage-specific biomarkers, such as atrophy or amyloid deposition, seem to hold best promises in AD diagnostic and subsequent treatment.

3 | RELATIONSHIPS BETWEEN THE TPJ AND THE DMN

Due to the TPJ's multifaceted role in cognitive function and its involvement in different networks, the region draws speculation to its function within the DMN. Although there is variability in what is considered part of or a subregion within the TPJ, the literature largely suggests that it includes the posterior superior temporal sulcus (pSTS), the lateral occipital cortex (LOC), the middle temporal gyrus (MTG), and multiple regions within the inferior parietal lobule (IPL) like the angular gyrus (AG) and the supramarginal gyrus (SMG) (Igelström & Graziano, 2017; Mars et al., 2012).

Using diffusion-weighted tractography-based parcellation, Mars et al. (2012) divided the TPJ into three subregions (a dorsal IPL region, and two ventral TPJ regions, namely TPJa and TPJp) and then computed resting-state functional connectivity analyses from each subregion.

The posterior part of the ventral TPJ subregion (TPJp) displayed strong connectivity with the core areas of the DMN (PCC, anterior medial PFC (amPFC), and precuneus), whereas the other two subregions did not show much connectivity with the DMN. Other work has divided the right TPJ in two distinct clusters (anterior (aRTPJ) and posterior (pRTPJ)) functioning as complementary antagonistic mechanisms related to external or internal oriented processing (Bzdok et al., 2013). Using a multimodal fMRI parcellation paradigm, the authors extended previous findings suggesting the pRTPJ region as functionally connected with the DMN. Moreover, Igelström et al. (2015) used resting-state fMRI and employed independent component analyses to identify five bilateral subdivisions of the TPJ. Anatomically, they described these as the TPJd, TPJv, TPJa, TPJc, and TPJp which includes the intersection between the posterior superior temporal and ventral parietal lobes. The right TPJp demonstrated connectivity to regions resembling that of the DMN, deepening evidence of region-specific TPJ function within the DMN. There were some overlap regarding the different areas referred to as the posterior TPJ. Mars et al. (2012) referred the posterior TPJ to the MNI coordinates of 54, −55, 26, Bzdok et al. (2013) noted 54, −54, 16.5, whereas Igelström et al. (2015) relayed three data sets placing the posterior TPJ at 60, −51, 15; 63, −51, 15; and 63, −48, 24. Despite these relatively consistent findings, the true role of the TPJ, namely the posterior region, remains vague in how this subregion interacts within the DMN.

Although Buckner et al. (2008) initially identified the TPJ as integral part of the dmPFC subsystem, the following study instead classified the TPJ as a region that couples with the DMN only during specific tasks. Using fMRI during a working memory paradigm, the authors found high connectivity between the TPJ and DMN during memory encoding but not sustained during the presentation of distractors, possibly indicating the TPJ's ability to act independently of the DMN (Anticevic et al., 2010). In addition, coactivation of the DMN, particularly the anterior mPFC, and the TPJ during social cognition has been particularly highlighted (Overwalle, 2009). Whether the TPJ is an integral component of the dmPFC subsystem or functionally independent from the DMN, further work exploring the relationship between the TPJ and the DMN, as well as with other large-scale brain networks, may provide meaningful insight for higher cognitive processes.

4 | INTERRELATIONSHIP BETWEEN ANOSOGNOSIA, TPJ AND DMN IN AD

4.1 | Anosognosia and the TPJ in AD

Neuroimaging studies consistently associate TPJ areas with the symptom of anosognosia. Sedaghat et al. (2010) compared SPECT scans of AD patients with and without anosognosia and found that AD-anosognosia patients demonstrated reduced rCBF in the right inferior parietal areas, and in the left and right medial temporal cortex. Moreover, analysis between mild- and moderate-AD groups with anosognosia highlighted reduced rCBF specifically within the right inferior parietal area, a TPJ region. The Pr. Salmon's team also provided several pieces of evidence that reduced metabolic activity in the TPJ may be related to AD-anosognosia. Interestingly, they reported TPJ hypoactivity to be associated with anosognosia-related discrepancies in the judgment of the patient's clinical status between the patient and their caregiver in cases of mild and mild-to-moderate AD (Salmon et al., 2005a, 2005b, 2006). During a go/no-go task, Amanzio et al. (2011) assessed two groups of AD patients (described as unaware or aware). Comparing functional neural activity from the aware-AD patients, the unaware cohort exhibited hypoactivity in regions of the cingulate (part of the DMN) and temporoparietal regions (Brodmann area 39), particularly lateralized to the right hemisphere. Tagai et al. (2018) collected SPECT images from 37 patients with mild AD or MCI due to AD with scores on the Anosognosia Questionnaire for Dementia. Differentiating these groups with healthy age-matched control showed anosognosia severity associated with higher rCBF in the left TPJ. These authors propose that higher rCBF of the left TPJ acts as a compensatory mechanism for the aspects of outdated autobiographical memory retrieval in an attempt to “resist” anosognosia. However, the authors did note that the higher rCBF within the left TPJ in AD patients was not higher than that of healthy controls.

4.2 | Anosognosia and the DMN in AD

Cortical and DMN dysfunction has been shown to be particularly severe in AD patients with anosognosia. The reviews of neuroimaging studies have implicated anosognosia with patterns of hypoactivity in medial temporal and parietal regions, the right temporoparietal cortex, and various areas associated with the DMN or other areas of convergence linked to self-referential and cognitive-related processes (Mondragón et al., 2019; Starkstein, 2014). Antoine et al. (2019) used fMRI resting-state connectivity in different patient samples to observe modifications of default mode subnetworks related to anosognosia. The study found significant disconnection between and within DMN subsystems, which was associated with memory-related anosognosia in AD, implicating the dorsomedial subsystem and particularly the MTL subsystem, and TPJ-related regions such as the IPL and the MTG. In addition to a strong relationship between dysfunctional DMN connectivity and AD, there also appears to be a significant association between anosognosia in AD and exceptionally disrupted communication between self-related and memory-related brain networks (Perrotin et al., 2015). PET scans of AD patients with anosognosia reveal hypometabolism of the cortical midline structures and fronto-temporal dysfunction while fMRI paradigms tend to demonstrate reduced within-network connectivity in DMN hubs (Mondragón et al., 2019). This indicates a general trend for DMN architecture to be profoundly disturbed in AD, and especially in those who experience anosognosia.

4.3 | Anosognosia prevalence and AD

Research examining the prevalence of anosognosia in AD provides mixed findings. Castrillo Sanz et al. (2016) conducted a prospective observational study on 97 patients with AD which unveiled the prevalence of anosognosia in approximately 71% of their studied patients. Using a multivariate analysis, they found an association of anosognosia with less education, more behavioral difficulties, and older age. A bivariate analysis shown that worse performance on cognitive and global testing scores reflected greater prevalence of anosognosia. Interestingly, their work did not share previous findings associating anosognosia with greater caregiver burden. Moreover, a longitudinal study conducted by Starkstein et al. (1997) assessed changes in depression and anosognosia in 116 patients with AD from an initial evaluation to a follow-up evaluation 1–2 years. At baseline, 39% of patients demonstrated the characteristics of anosognosia and follow-up visits highlighted that as AD progresses, the impact of anosognosia increases significantly in addition to cognitive decline, increase in depression, and impairment in activities of daily living. Notably, the follow-up sample only included approximately half of the initially enrolled subjects, as some became deceased, or were unable to be evaluated for other reasons (e.g., lost to follow-up, caregiver refused). While the occurrence of anosognosia in AD is considerable, more delicate and longitudinal research is needed to assess the true prevalence and impact of anosognosia.

4.4 | Interrelationship between anosognosia, AD, and the TPJ

Progress in neuroimaging research supporting investigations of large-scale brain networks have shed light on the TPJ as a region of interest for AD and AD-DMN dysfunction, particularly in the case of anosognosia. While exploration of the variable TPJ dynamics within the AD spectrum remains ambiguous in its relation to the DMN, these recurrent findings offer insight into uncovering dysfunction leading to anosognosia. Considering the posterior TPJ's connectivity with the DMN (Igelström et al., 2015) and dmPFC subsystem (Andrews-Hanna, 2012), and diverse brain function (namely multimodal sensory integration (Matsuhashi et al., 2004), self-other distinction (Ruby & Decety, 2001), and embodiment (Lenggenhager et al., 2006)), it seems plausible that reduced activity and dysfunctional connectivity may facilitate an antagonistic relationship between the TPJ and DMN due to disease progression. Ultimately this may contend as a significant factor contributing to anosognosia in patients with AD.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Our goal was to begin piecing together the growing literature on the relationship between the TPJ and DMN in AD-related anosognosia. Although it is unlikely that TPJ dysfunction is the sole source for the manifestation of anosognosia, it is unclear how or when, or even if, TPJ modulation serves as a compensatory mechanism or a possible contributor to anosognosia. Additionally, a recent study by Meyer et al. (2019) proposed that a specific subtype of AD could be characterized by distinct hypometabolic activity of the TPJ. Of note, the authors mentioned the subtypes could only be distinguished by age and a select few non-memory neuropsychological testing scores compared to typical AD patients but were not dissociated by the clinical evaluation, which may not have been sensitive enough to detect such distinctions. It is currently unknown how this AD subtype may relate to anosognosia. Longitudinal studies of patients with AD carefully examining cognitive status and sensitive assessments of anosognosia combined with various neuroimaging modalities hold great promise in continuing to evolve our understanding in how the TPJ operates within the DMN in relation to the feature of anosognosia.

CONFLICT OF INTEREST

All the authors involved in this article report having no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, L.L., A.S., and I.B.; *Writing – Original Draft*, L.L. and A.S.; *Writing – Review & Editing*, L.L., A.S., S.H., and I.B.; *Supervision*, I.B.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

Transparent Peer Review Report

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