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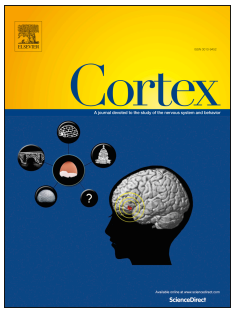

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Neural correlates of impaired cognitive processes underlying self-unawareness in Alzheimer's disease

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ABSTRACT

Self-unawareness concerning current symptoms remains a clinical challenge in Alzheimer's disease. Reduced self-awareness likely depends on complex biopsychosocial mechanisms that comprise multiple cognitive processes, regulated by personal goals and values. We specifically reviewed the cognitive processes impaired in unaware participants with AD by emphasizing the related impaired brain activity observed during task-based fMRI. Unawareness can be explained by a failure in functioning of or in connection between brain regions that intervene in access, retrieval and updating of (present or extended) self-information (posterior midline, medial temporal, inferior parietal cortices), or in its monitoring, evaluation, or control (medial and lateral prefrontal cortices). Although one must be cautious when relating function to brain regions, impaired processes were tentatively related to the Cognitive Awareness Model. Although brain function depends on neural networks, impaired brain activity during cognitive processes was discussed according to previous studies reporting correlations between brain regions and scores of anosognosia. The review provides a framework to help clinicians considering processes that can explain unawareness in dementia. In patients at early stages of AD, different levels of awareness of cognitive or social clinical changes might be described as impairment in the interaction between specific cognitive processes and contents.

Key words: Alzheimer, self, unawareness, anosognosia, metacognition, perspective taking

1. Introduction

Unawarenes of deficits can be assessed by evaluating specific processes supporting self-awareness and/or by calculating discrepancy scores to rate the intensity of unawareness. Previous reviews reported changes in brain regions correlated to the presence or the degree of anosognosia or metacognitive metrics in Alzheimer's disease (AD). Zamboni and Wilcock observed that altered frontal and temporo-parietal regions were the main neuro-anatomical correspondents of unawareness in dementia, while Chavoix and Insausti reported that different structures of the medial temporal lobe are involved in impaired self-awareness depending on the domain of interest in different types of dementia (Chavoix & Insausti, 2017; Zamboni et al., 2013). Mongragon et al. performed a meta-analysis of articles using functional neuroimaging and emphasized impaired connectivity in the default mode network of anosognosic participants with AD. They also reported dysfunction of midline cortical structures in early stages of anosognosia in mild cognitive impairment (MCI) and AD, followed by impaired parietotemporal activity and later by frontotemporal involvement (Mondragon, Maurits, & De Deyn, 2019). In a systematic review, 8 key regions were associated with anosognosia scores in AD: the medial temporal lobe, the anterior cingulate cortex and the inferior frontal gyrus, and also the superior frontal gyrus, medial frontal gyrus, orbitofrontal cortex, posterior cingulate cortex, and the insula (Hallam, Chan, Gonzalez Costafreda, Bhome, & Huntley, 2020). The arguments for mnemonic anosognosia were recently reviewed, and several processes studied in AD were related to components of the Cognitive Awareness Model (CAM) (Lenzoni, Morris, & Mograbi, 2020). In our narrative review, we capitalized on this literature, but we aimed to focus on the neural correlates of specific cognitive processes impaired in

patients with reduced awareness of their clinical status, such as monitoring, evaluating, perspective taking, updating and metacognitive processing. We first introduce cognitive processes involved in models of self and awareness. We describe cognitive processes impaired in unaware participants with AD to subsequently review their neural correlates. Processes and their correlates are tentatively referred to the Cognitive Awareness Model. Research and clinical perspectives of the framework are finally discussed.

2. Processes involved in the self concept

2.1. Different levels of self processes

The self is a multi-dimensional concept comprising different levels, such as (lower-level) awareness of one's perceptions and current actions, and (higher-level) awareness of one's projects, related to one's goals, values and beliefs (Clare, Markova, Roth, & Morris, 2011; Gil et al., 2001). Accordingly, an individual may entertain lower-level self-awareness of a behavior without evaluative process, while reflexive self-awareness occurs when the content of one's observation is one's own thoughts and behavior (Prebble, Addis, & Tippett, 2013). At a higher-level, individuals who are able to conceptualize themselves can also evaluate others' mental state and take a third-person perspective on the self (Marcel, Tegner, & Nimmo-Smith, 2004). The differentiation between self and other may be seen as a central feature of self-awareness (Lewis, 2011; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008). For example, one's own name is part of self-knowledge for which the central

feature is the designation of certain stimuli as being self-representative (Northoff, Qin, & Feinberg, 2011).

2.2. Self and long term memory

Long term memory systems have also been distinguished by different levels of consciousness and relationship to the self (Markowitsch & Staniloiu, 2011; Tulving, 1985). Semantic memory represents general facts and knowledge, including about oneself (i.e., personal semantics). One has access to this context-free knowledge through noetic consciousness, providing semantic self-continuity. Episodic autobiographical memory (EAM) corresponds to events that a subject can recollect and re-experience while "travelling" in subjective time with autonoetic consciousness, providing phenomenological self-continuity (Addis & Tippett, 2008; Piolino, 2003; Prebble et al., 2013). Recent views suggest that episodic and semantic memory overlap and interact to a large extent (Renoult, Irish, Moscovitch, & Rugg, 2019).

2.3. Different components of self

In a social-cognitive approach, the self was partitioned in different components comprising EAM, knowledge of facts about personal life and also representations of own personality traits (Klein & Gangi, 2010; Klein, Rozendal, & Cosmides, 2002). Moreover, the self also relies on interoception (a sense of internal body state), on a sense of personal agency and ownership, and on the (high-level) ability for self-reflection (Mograbi, Huntley, & Critchley, 2021). Klein and colleagues emphasized that the different components need to adequately interact to provide a sense of

"unitary self". Other authors have also distinguished structural (self-knowledge) and functional components (self-awareness processes) of the self (Northoff et al., 2011; Prebble et al., 2013). Like so, a self-memory system has been described, that comprises a component called the working-self (Conway, 2009; Conway & Pleydell-Pearce, 2000). This is a central executive structure that processes information (recollection, regulation, updating) according to our current goals for decision making about our behavior. It takes into account (implicitly or explicitly) emotions, personal beliefs and values, and it interacts with autobiographical memory. The system is functioning according to principles of maintenance of self-continuity (self-coherence) and adaptation to changes (self-adjustment). Accordingly, our personal schemes and values will influence the selection by the working-self of new information entering AM. During retrieval, the self-related selection is consistent with the principle of memory reconstruction, since it will influence the process of re-creation of an experience stored in memory according to current perceptions, social circumstances and general knowledge (Moscovitch & Winocur, 1992). Consequently, there is an ongoing dynamic process of selection of new memories and updating of personal knowledge guided by working-self processes. Importantly, personality traits may be preserved despite EAM impairment and they may be updated without conscious recollection of representative events (Klein, Loftus, & Kihlstrom, 1996).

2.4. The Cognitive Awareness Model

The most influential model of awareness of cognitive functioning is the Cognitive Awareness Model (CAM) (Agnew & Morris, 1998; Morris & Hannesdottir, 2004; Morris & Mograbi, 2013). In this model, information concerning current cognitive

functioning (“I lost my hat”) goes through perception components (with low-level awareness) and enters recent memory systems (short term and episodic memory). Information may be compared in an executive comparator system to self-information stored in a Personal Database (PDB, that contains semanticized conceptual knowledge) and an Autobiographical Conceptual Memory System (that comprises lifetime scenarios and events) allowing one to have a representation of one’s own capacities (e.g., “I am very organised”). The comparator mechanisms (CMs) have also access to a Generic Memory System that contains general semantic information (for example on others). While comparison requires different cognitive processes initially performed with a self-perspective, a third-person perspective (looking at ourselves through the eyes of others) may be used to complement our self-knowledge (Wilson & Dunn, 2004). So, different processes dynamically intervene in the CMs, and the output can be further treated by higher level Metacognitive Awareness mechanisms, that allow us to make an explicit self-reflexion and to take a decision (“I should check where I put my hat”). Metacognition refers to monitoring and regulation of one’s own cognitive processes. An influential model of metacognition comprises a meta-level that receives information from a lower (object) level through a monitoring process, and the meta-level regulates the object-level through a control process (Nelson & Narens, 1990). Interestingly, the CAM comprises different levels of metacognitive processes (Seow, Rouault, Gillan, & Fleming, 2021), from local task monitoring in CMs to global metacognitive awareness mechanisms and also to metacognitive beliefs in the PDB. In the CAM, when monitoring or evaluative processes detect a mismatch between current information and personal knowledge, an updating process may modify (and partially reconstruct) the database. Although the model essentially describes self-reflection, the output of the CM may be

automatically treated to regulate our behavior and implicit self-awareness may dissociate from explicit self-awareness (Geurten, Salmon, & Bastin, 2021; Mograbi & Morris, 2013).

3. Impaired cognitive components of self-awareness models in Alzheimer disease

Impaired self-awareness or anosognosia corresponds to the reduced subjective experience of a clinical disturbance (Prigatano, 2009). Impaired self-awareness has been mostly measured through discrepancy scores comparing the patient's evaluation of self-performance with either a relative's evaluation or an objective measure of performance (Kalbe et al., 2005; Klein et al., 1996; Morris & Hannesdottir, 2004; Salmon et al., 2006; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). Self- versus informant-rating is a score related to explicit evaluative processes, while self-rating versus performance relates to metacognitive monitoring metrics (Berlingeri et al., 2015). In Alzheimer's disease, anosognosia for cognitive impairment is frequent, while impaired (lower-level) awareness of one's body representation in space, sense of personal agency and ownership or impaired self-awareness of one's social identity are rare (Gil et al., 2001; Mograbi et al., 2021).

3.1. Impaired memory processes

We already emphasized that AM normally contributes to the sense of continuity of identity (Addis & Tippett, 2004; Conway, 2009). In the early dementia stage, EAM is

more affected than personal semantic knowledge (Eustache et al., 2004; Piolino et al., 2003). The “noetic consciousness” of premorbid personality traits is relatively preserved even in severe AD stage, and it was hypothesized to depend on abstract summaries kept in personal semantic memory (Klein et al., 2002). However, the strength of identity is weaker in AD (Addis & Tippett, 2004). For example, patients at severe stages of AD were shown to be impaired in recognizing themselves in a mirror (Biringer, Anderson, & Strubel, 1988; Grewal, 1994). This might correspond to impaired matching of an image to a self-representation, without introspection, but it might also be related to impaired self-awareness (and impaired third-person perspective on self). In the CAM, a mismatch between the visual input and the self-representation would lead aware patients to provide a metacognitive judgment of self-modification (“I changed”), while unaware patients could keep seeing a stranger in the mirror. In Conway’s model, the working-self is able via gating mechanisms to exert a positive control bias on self-coherence, while lowering the influence of self-adjustment (Conway, Singer, & Tagini, 2004). Self-coherence would maintain personal semantic information that preserves self-identity of patients with AD, while loss of EAM would impair recollection of recent information, such as events linked to a negative social representation. In the CAM, impairment in EAM and relative sparing of semantic memory in AD would lead to an outdated sense of self (Mograbi, Brown, & Morris, 2009). Accordingly, the self is reaffirmed in personal stories where former selves are components of current identity (e.g., the person keeps repeating always the same old stories) (Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish, 2019). However, participants with early AD do not simply refer to previous personality traits to provide judgment on current personality, they may provide new, distorted judgments compared to their relatives (Jedidi et al., 2013).

3.2. Impaired executive processes

Lack of awareness for memory impairment has been related to impaired effortful retrieval monitoring processes, and not to performance on (easier) memory tests (Gallo, Chen, Wiseman, Schacter, & Budson, 2007). Accordingly, several studies have shown that impaired source monitoring or impaired metacognitive processes are more important than memory accuracy in explaining cognitive anosognosia in AD (Cosentino, Metcalfe, Butterfield, & Stern, 2007; Dodson et al., 2011; Gallo et al., 2007; Souchay, 2007). Importantly, when performing multiple trials, some participants with AD are able to improve their rating of performance just after recall or their prediction of subsequent task performance immediately after feedback, an ability which is mostly lost after delay (Ansell & Bucks, 2006; Mimura & Yano, 2006; Moulin, Perfect, & Jones, 2000), even after a memory training program (Silva, Pinho, Macedo, Souchay, & Moulin, 2017). In the context of CAM, new information coming from feedback would enter working or immediate memory and be consciously processed by comparator mechanisms, but it would fail to be consolidated into long-term memory (leading to mnemonic anosognosia). Importantly, one must keep in mind that impaired awareness of dysfunction is variable in patients with clinically probable AD.

4. Neural correlates of self-related cognitive processes in unaware patients with AD

4.1. Neural correlates of self-appraisal

A functional MRI (fMRI) task-related study of self-relevance judgments revealed that participants with AD activated the ventromedial prefrontal cortex (VMPFC) as elderly control (EC) subjects did (Genon et al., 2014). The VMPFC is involved in the evaluation and assignment of personal significance and value to self-related contents (D'Argembeau, 2013). VMPFC activation during self-referential judgments did not provide long-term advantage for subsequent episodic retrieval in participants with AD (Genon et al., 2014). Consistently, in another fMRI self-appraisal task using trait adjectives, participants with mild cognitive impairment (MCI compared to EC) showed only minimally attenuated activity in the anteromedial prefrontal (AMPFC) and the posterior cingulate cortex (PCC) (Ries et al., 2007). However, controlling for the extent of memory impairment, a regression analysis revealed that the higher the anosognosia discrepancy score, the lower the AMPFC and PCC activation during self-evaluation. To better understand the evaluative process of self-information in the CAM Comparator System, it is interesting to emphasize that default mode network (DMN) regions, namely AMPFC, PCC, and left inferior parietal lobule (IPL), were identified in a large sample of young control participants performing an fMRI self-appraisal task with trait adjectives (Davey, Pujol, & Harrison, 2016). In the optimal model obtained with dynamic causal modelling, self-appraisal processes were driven by PCC activity involved in the retrieval and integration of mental representations (Cavanna & Trimble, 2006) and moderated by the regulatory influences of MPFC involved in directing ongoing thought processes (Burgess, Dumontheil, & Gilbert, 2007; Moran, Kelley, & Heatherton, 2013) to facilitate self-reflection (Kim, 2020). Accordingly, anosognosia for memory impairment in MCI would be related to both decreased integrative access to present and extended self-information via PCC

functions (and via IPL that plays a role in retrieving and selecting complex memory information) and decreased regulatory gating of self-information into conscious awareness via the MPFC. The proposal is in line with a metacognitive experiment performed in participants with AD (Mimura & Yano, 2006). Patients overestimated their performance at a classical memory task. They did not incorporate feedback information into their personal database since postdiction (monitoring of performance) after a second trial showed again overestimation. The degree of postdiction failure was correlated to cerebral blood flow in VMPFC, PCC and the ventrolateral prefrontal cortex (VLPFC). An interpretation is that impaired PCC functioning did not provide integrative access to recent (poorly encoded) information on performance, that was neither correctly monitored by the VLPFC, nor adequately gated by the VMPFC to assign a motivated value. During another metamemory task, inadequate pessimistic prediction of participants with AD was negatively correlated with gray matter volume in VLPFC and also in medial temporal lobe (MLT) and PCC (Genon et al., 2016). In the CAM, lesioned VLPFC in AD would impair local monitoring of own cognitive performance, poorly informed by dysfunctional MLT and PCC. Interestingly, the more rostral VLPFC was shown to be recruited when healthy participants were instructed to provide higher level, global control of their own thoughts (McCaig, Dixon, Keramatian, Liu, & Christoff, 2011; Schaefer et al., 2003), and it was recruited during experiential (present) self-focus (Farb et al., 2007), suggesting a role of anterior VLPFC in metacognitive coordination of self-referential processes (Fleming & Dolan, 2012; Morales, Lau, & Fleming, 2018).

4.2. Self and other-perspective

Self-appraisal was contrasted to other-appraisal of trait adjectives in two studies of participants with AD compared to EC (Ruby et al., 2009; Zamboni et al., 2013). The dorsomedial prefrontal cortex (DMPFC) and the dorsal anterior cingulate gyrus (DACC) were respectively less activated in AD than in controls for self- versus other-evaluation. DACC activity correlated to anosognosia discrepancy scores (Zamboni et al., 2013), and DMPFC glucose metabolism was also correlated with anosognosia for self-personality traits (Jedidi et al., 2013). Activation for metacognition and for theory of mind was shown to overlap in the DMPFC in a meta-analysis (Vaccaro & Fleming, 2018) and DMPFC was activated for the interaction of third person perspective on self (D'Argembeau et al., 2007). DMPFC activity was recently proposed to be the neurobiomarker of self-focused attention as it uniquely occurs during performance of top-down self-reference tasks rather than during resting state (Frewen et al., 2020). The data consistently suggest that patients with unawareness use less self-focused attentional reflective processes than controls to perform self-appraisal and would benefit less from top-down modulation by Metacognitive Awareness mechanisms in the CAM.

When participants with AD assessed their own (vs. their relative's) personality traits, significant fMRI activation was detected in the intraparietal sulcus (IPS) in both hemispheres (Ruby et al., 2009). The IPS was involved in self-processing (Kircher et al., 2000; Ochsner et al., 2005) and was activated for familiarity-based judgments during recognition tasks (Genon et al., 2013). The data suggest that IPS activation during self-personality assessment in AD is associated with familiarity-based retrieval of non-updated personal semantic representations (Klein, Cosmides, & Costabile, 2003).

Patients with AD have impaired third-person perspective (Jedidi et al., 2013). When participants with AD tried to take a third-person perspective to provide judgment on relevance of adjective traits (independently of the target, self and other), activation was detected in the posterior part of the DMPFC (Ruby et al., 2009). The pDMPFC was recruited for attentional processing involved in inferring mental states (Calarge, Andreasen, & O'Leary, 2003; D'Argembeau et al., 2007; Mitchell, Macrae, & Banaji, 2004; Ruby & Decety, 2004; Walter et al., 2009). However, recruitment of pDMPFC in participants with mild AD is not efficient since they are making errors when taking their relatives' perspective. The inability of patients to adequately select and control information during inferring processes, i.e. recent memories (such as complaints of the relative about personality changes) more than past (non-updated) memories on self-personality may be one of the reasons why perspective taking fails in patients with AD. Another mechanism related to perspective-taking impairments in AD would be a failure of the dynamic translation and selection process between the egocentric (first-person perspective) and allocentric (third-person perspective) viewpoints (Morganti, Stefanini, & Riva, 2013; Serino, Cipresso, Morganti, & Riva, 2014) for which the retrosplenial cortex (RSC, impaired in AD) was assigned a crucial role (Byrne, Becker, & Burgess, 2007; Serino & Riva, 2017).

In the literature, other-referential processes may produce greater response than self-appraisal within the DMPFC and in the temporoparietal junction (TPJ) (Frewen et al., 2020). The TPJ is a key region of the "social brain", it contributes to representations of the self (Lattanzio, Seames, Holden, & Buard, 2021) and it is involved in object level comparison processes (Jiang, Wang, & Wan, 2022). The different correlations between anosognosia scores and DMPFC or TPJ in the literature (Jedidi et al., 2013; Salmon et al., 2006) are consistent with a meta-analysis which found the TPJ to be

involved in inferring concrete, present states (such as evaluating recent cognitive functioning), while the DMPFC was involved in inferring people's social, enduring dispositions (such as the evaluation of personality traits) (Van Overwalle, 2009). A better understanding of the role of the TPJ comes from a multilevel mediation analysis performed on fMRI data recorded during a self-appraisal task on trait adjectives (Knyazev, Savostyanov, Bocharov, Levin, & Rudych, 2020). A positive mediation effect between adjective traits and response was found in the TPJ. The mediating role of the TPJ suggests that it might be involved in the retrieval of currently relevant (other and self) memories, to be supplied to the DMPFC associated with higher level attention control (Gusnard, Akbudak, Shulman, & Raichle, 2001; Mitchell, 2008).

4.3. Updating self-information

We already reported that anosognosia concerning current capacities might be related to overreliance on outdated self-knowledge. Metamemory processes monitor information introduced during episodic retrieval, with respect to existing retrieval goals, before knowledge updating occurs. One possible framework for describing updating of personal knowledge is episodic updating (Finn, 2017; Garland, Vaidya, Tranel, Watson, & Feinstein, 2021). In young participants, anterior hippocampus and VMPFC were related to the updating processes for highly relived recent memories (St Jacques, Olm, & Schacter, 2013). The update of self-knowledge through memory processes such as recollection of personal experiences and consolidation was suggested to be the main function of the MTL in the self-awareness network (Chavoix & Insausti, 2017). Consistent with episodic and semantic AM overlap (Renoult et al.,

2019), better recollection of episodes from early adulthood was correlated with a less severe anosognosia in AD, suggesting an association between the progressive loss of EAM and deterioration of the PDB (Berlingeri et al., 2015). In the field of egocentric spatial information (coding for self-to-object relations), the egocentric-updating processes are defined as dynamic changes in both head orientation and observer's spatial position (Farrell & Robertson, 1998). Egocentric updating revealed an activation of the right hippocampus, highlighting the importance of the MTL for self-location updating (Gomez, Cerles, Rousset, Remy, & Baciu, 2014). In an interesting study, patients with AD performed a metacognitive experiment comprising prediction, task performance, global comparison when participants estimate whether they performed according to the prediction (via evaluative processes), post-diction (via monitoring and evaluative processes) and a post-study prediction (Berlingeri et al., 2015). In an episodic memory task, initial and post-study prediction scores for memory performance were positively correlated in patients with anosognosia, suggesting that prediction mainly relied on the PDB, that was not updated by recent information on own memory impairment. Most patients who continued to overestimate themselves in the post-study prediction phase failed in the post-diction task. The more severe the anosognosia, the weaker the functional connectivity between the left middle temporal cortex (MIDTC) and the left MTL. The MIDTC has been reported as a key region for the PDB (Svoboda, McKinnon, & Levine, 2006; Tacikowski, Berger, & Ehrsson, 2017) and MIDTC activity was decreased in AD versus controls during self- versus other-appraisal tasks using trait adjectives (Zamboni, 2013). The impaired connectivity related to the degree of anosognosia (overestimation of prediction compared to performance) was suggested to represent

the neural counterpart of the inability to associate (and update) self-representations stored in the PDB with new information related to the current memory task in MLT.

5. Discussion on brain correlates of clinical unawareness

The CAM capitalizes on well-established cognitive and neuropsychological data and it has the advantage to provide a framework for understanding unawareness of clinical status in patients with AD (Amanzio et al., 2011; Chavoix & Insausti, 2017). We will discuss previous correlation studies between brain regions and the severity of unawareness in the light of cognitive processes highlighted in this review and tentatively represented in Figure 1.

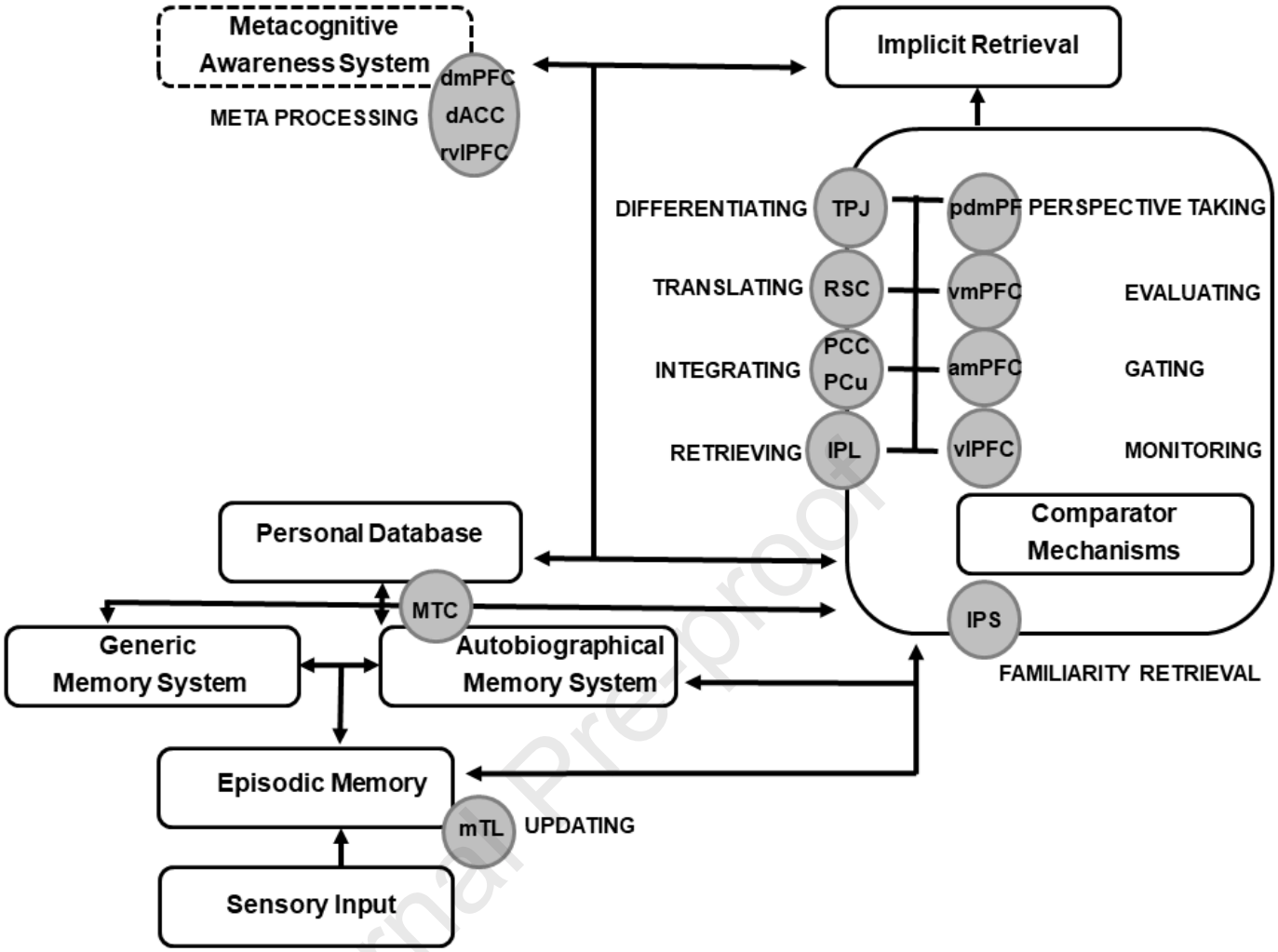

Figure 1. Neural correlates of cognitive processes in the Cognitive Awareness Model

mTL= medial temporal lobe (St Jacques, 2013; Chavoix, 2017); MTC= middle temporal cortex (Zamboni, 2013; Berlingeri, 2015); IPS= intraparietal sulcus (Ruby, 2009); IPL= inferior parietal lobe (Davey, 2016); PCC/Pcu= posterior cingulate cortex/precuneus (Mimura, 2006; Ries, 2007); RSC= retrosplenial cortex (Byrne, 2007); TPJ= temporo-parietal junction (van Overwalle, 2009; Knyazev, 2020); vlPFC= ventrolateral prefrontal cortex (Mimura, 2006); amPFC= anteromedial prefrontal cortex (Ries, 2007); vmPFC= ventromedial prefrontal cortex (Mimura, 2006; Genon, 2014); pdmPF= posterior dorsomedial prefrontal (Ruby, 2009);

dmPFC= dorsomedial prefrontal cortex (Ruby, 2009); dACC= dorsal anterior cingulate cortex (Zamboni, 2013): rlPFC= rostrolateral prefrontal cortex (McCaig, 2011)

5.1. Impaired comparator and metacognitive mechanisms in AD

There is not much difference in activation of VMPFC and AMPFC between participants with AD and controls during self-reference tasks. Although a priori surprising, the observation is consistent with the similarity of default mode network (DMN) activation for AM retrieval in AD and controls (Meulenbroek, Rijpkema, Kessels, Rikkert, & Fernandez, 2010). However, correlation analyses show that more unawareness is related to relatively lower involvement of the MPFC in evaluating (explicitly or implicitly) self-value of current stimuli ("Am I losing objects so frequently?") or in selecting (gating) information for self-referencing (Figure 1). Grey matter atrophy in the medial orbitofrontal cortex, close to the VMPFC was also inversely correlated to unawareness measured as impaired self-appraisal accuracy on cognitive tasks (Rosen et al., 2010). The authors suggested that the established role of orbitofrontal regions in emotional self-evaluation is consistent with the idea that self-processes in VMPF structures are influenced by personal values and emotional factors, such as current feelings and motivation (Clare et al., 2011; Rosen, 2011).

VMPFC and AMPFC activity is frequently related to that in PCC, which plays a role in integration and comparison of current information with self-memories, a function of the CAM-CMs (Figure 1). VMPFC and PCC activity was correlated to a high degree

of confidence in control participants (Qiu et al., 2018). Impaired connectivity between those anterior and posterior medial brain regions in resting state is consistently correlated to the degree of anosognosia in AD (Antoine et al., 2019; Perrotin et al., 2015; Vannini et al., 2017). Posterior midline cortices specifically show decreased resting glucose metabolism in patients at early AD stages lacking awareness of their memory impairments, compared to patients aware of their deficits (Nobili et al., 2010; Vannini et al., 2017). Referring to the CAM, the integrative function of the PCC would be necessary to gather current and past information on clinical status, which would be gated by VMPFC to provide an evaluative judgment ("I Am losing objects more frequently than I did before"; Figure 1).

Lack of awareness has been explained in the literature by a failure of monitoring and control processes (Cosentino et al., 2007; Souchay, 2007). There are different levels of monitoring in the CAM: VLPFC does support local monitoring processes of the CMs during self-reference tasks and DLPFC was related to metacognition activity in a composite meta-analysis of control subjects (Vaccaro & Fleming, 2018). DMPFC and DACC activity, involved in higher meta processes for self-referencing (related to Metacognitive Awareness mechanisms in the CAM), is consistently decreased in patients with unawareness of clinical impairment (Guerrier et al., 2018; Jedidi et al., 2013). DACC might be preferentially involved in cognitive and DMPFC in social meta-processes (Jiang et al., 2022). However, even when DMPFC is impaired, self-referential processes remain flexible, and participants with AD can use familiarity-based judgment supported by IPS instead of higher metacognitive processes (Figure 1).

Finally, in the CAM, patients with AD who are unable to take a third-person perspective on self would not benefit from other knowledge (in the Generic Memory

System) when asked to evaluate their abilities (“my relative says I lose memory, but I think he exaggerates”) (Morris & Mograbi, 2013). In a meta-analysis on theory of mind (attributing mental state to ourselves or others), clusters of activation were reported in the MPFC and the TPJ (Molenberghs, Johnson, Henry, & Mattingley, 2016). DMPFC and TPJ are both part of a subnetwork of the DMN (Andrews-Hanna, Smallwood, & Spreng, 2014). The TPJ was shown to be important to differentiate between self and other (Samson, Apperly, Chiavarino, & Humphreys, 2004) and it would be involved in local processing of current information, while DMPFC would support meta-representation, a higher awareness level (Clare et al., 2011) (Figure 1).

5.2. Impaired self-knowledge in AD

Concerning past (semanticized) personal knowledge, the MIDTC and the temporal pole are part of the same DMN subnetwork and activity in those regions is supposed to be related to access to the PDB in the CAM (Berlingeri et al., 2015; Svoboda et al., 2006). PDB is outdated in patients with anosognosia (Morris & Mograbi, 2013). Accordingly, in the frontotemporal dementia literature, decreased temporal pole activity plays an important role in disturbance of personal semantic memory and self-schemas (Ruby et al., 2007).

Concerning current and episodic information, MTL is part of the memory subnetwork of the DMN (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). The region is important for AM (Morris & Mograbi, 2013; Piolino, Desgranges, & Eustache, 2009), along with cortical regions, such as the VMPFC (Bonnici et al., 2012; McDermott, Szpunar, & Christ, 2009). Hippocampal damage was related to loss of autobiographical memory in AD (Eustache et al., 2004; Philippi et al., 2012).

Self-assessment of cognitive functioning was correlated to MTL metabolism in a large population of patients with AD (Salmon et al., 2006). Since memory performance was taken as confounding variable, a mnemonic account for impaired awareness of self-cognition could not fully explain the observed results. An alternative explanation would be that MTL participates in the comparator process between external stimuli (such as the question “does it sometimes happen that you forget information”?) and information in the PDB (Gray, 1995; Vinogradova, 2001). Impaired MLT functioning would also be related to impaired updating of self-knowledge (Chavoix & Insausti, 2017) (Figure 1). Importantly, some patients with impaired episodic memory can (imperfectly) update their personal database (Jedidi et al., 2013), although most patients cannot (Klein & Gangi, 2010; Mograbi et al., 2009).

6. Conclusions

The main limitation of Figure 1 is that it must be kept in mind that there is neither an easy definition of the self (Klein & Gangi, 2010), nor a brain centre for awareness, that is rather conceived as an emergent property of activity in multiple brain regions (Morris & Mograbi, 2013). Since brain function depends on neural networks, one must also be cautious when relating function to brain regions, as in our adaptation of the Cognitive Awareness Model. In Figure 1, different kinds of information are shared between or integrated within different regions, as postulated in a recent integrative framework of self-awareness (Mograbi et al., 2021). The present review suggests that unawareness of clinical symptoms can be elucidated by assessing different types of failure in functioning of or in connection between brain regions that intervene in access to, retrieval and updating (posterior midline, medial temporal, inferior

parietal cortices), or in monitoring, evaluation and control of self and other information (medial and lateral prefrontal cortices), according to personal goals. Moreover, the CAM is consistent with hierarchical models of awareness (Chapman et al., 2018; Clare et al., 2011). Lower level self-awareness would occur in perception components (sensory input in Figure 1). Awareness of interoceptive states or body awareness is a core self-representation for which insula is frequently involved (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Farb et al., 2007; Gu, Hof, Friston, & Fan, 2013). Insular atrophy was related to memory unawareness (Cosentino et al., 2015; Hallam et al., 2020). Unawareness was interpreted as an impaired conscious detection of error and it might correspond to local monitoring in a perception component of the model. Subsequently, current information could be the object of further local awareness, for example when processed in TPJ (temporary self-other comparison) or in the precuneus for memory comparison (Jiang et al., 2022). Evaluation (via the VMPFC notably) would be a higher level of awareness, involved in stable representation of the self, while meta-processing would be the highest (global) awareness level for cognitive (DACC, RLPFC) or social (DMPFC) information.

Importantly, cognitive monitoring can also occur automatically, even in the DACC (Qiu et al., 2018), and the output of the comparator mechanisms in the CAM can implicitly regulate our behavior (Morris & Mograbi, 2013).

In AD, clinical evaluation can consider the dynamic interplay between access to information, diverse executive treatments in a comparator system, variable control, and dysfunctional updating of self-related information, as schematically illustrated in Figure 1. The hypothesis that unawareness emerges as a disconnection syndrome can be explored by connectivity analyses of neuroimaging or electrophysiological

data correlated to cognitive functions presented in the Figure. For example, evaluation of the theory of mind may provide information on perspective taking abilities of a patient (Ruby et al., 2009). Dysfunction of monitoring mechanisms leading to decrease of metacognitive error awareness can be detected by event-related potentials recorded with midline electrodes in early AD stage (Razafimahatratra et al., 2023). With such different tools, one may analyse the relative contribution of different processes in Figure 1 to the degree of unawareness of patients for their cognitive dysfunction. Understanding alteration in self-awareness in patient with dementia may also facilitate their clinical management. A third-person perspective taking might help some patients understanding their cognitive impairment (Bertrand, Landeira-Fernandez, & Mograbi, 2016). The demonstration of important error unawareness may justify erroless rehabilitation programs (Clare et al., 2000). It may also help clinicians to specify patient's capacities when assessing legal responsibilities. Finally, the framework is not limited to AD. In the behavioral variant of frontotemporal dementia (bvFTD) for example, impaired self-appraisal was related to VMPFC atrophy when cognition was assessed (Massimo et al., 2013), suggesting impaired evaluative processes. However temporal pole or TPJ degeneration was related to lack of awareness concerning daily behavior (Ruby et al., 2007; Zamboni, Grafman, Krueger, Knutson, & Huey, 2010), indicating impaired processing of autobiographical information. Accordingly, symptoms in different aetiologies of dementia must be related to diverse alterations within the network, determining different changes in self-awareness.

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Competing interests

The authors have no disclosure and they have no conflict of interest

References

Addis, D. R., & Tippett, L. J. (2004). Memory of myself: autobiographical memory and identity in Alzheimer's disease. *Memory, 12*(1), 56-74.

Addis, D. R., & Tippett, L. J. (2008). The contributions of autobiographical memory to the content and continuity of self: a social-cognitive neuroscience approach. In F. Sani (Ed.), *Self-Continuity: Individual and Collective Perspectives* (pp. 71-84). New York Psychology Press.

Agnew, S. K., & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: a review of the literature and a proposed model. *Aging Ment Health, 2*, 7-19.

Amanzio, M., Torta, D. M., Sacco, K., Cauda, F., D'Agata, F., Duca, S., . . . Geminiani, G. C. (2011). Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. *Brain, 134*(Pt 4), 1061-1076. doi: 10.1093/brain/awr020

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65*(4), 550-562. doi: 10.1016/j.neuron.2010.02.005

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann N Y Acad Sci, 1316*, 29-52. doi: 10.1111/nyas.12360

Ansell, E. L., & Bucks, R. S. (2006). Mnemonic anosognosia in Alzheimer's disease: a test of Agnew and Morris (1998). *Neuropsychologia, 44*(7), 1095-1102.

Antoine, N., Bahri, M. A., Bastin, C., Collette, F., Phillips, C., Balteau, E., . . . Salmon, E. (2019). Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum Brain Mapp, 40*(18), 5330-5340. doi: 10.1002/hbm.24775

Berlingeri, M., Ravasio, A., Cranna, S., Basilico, S., Sberna, M., Bottini, G., & Paulesu, E. (2015). Unrealistic representations of "the self": A cognitive neuroscience assessment of anosognosia for memory deficit. *Conscious Cogn, 37*, 160-177. doi: 10.1016/j.concog.2015.08.010

Bertrand, E., Landeira-Fernandez, J., & Mograbi, D. C. (2016). Metacognition and Perspective-Taking in Alzheimer's Disease: A Mini-Review. *Front Psychol, 7*, 1812. doi: 10.3389/fpsyg.2016.01812

Biringer, F., Anderson, J. R., & Strubel, D. (1988). Self-recognition in senile dementia. *Exp Aging Res, 14*(4), 177-180.

Bonnici, H. M., Chadwick, M. J., Lutti, A., Hassabis, D., Weiskopf, N., & Maguire, E. A. (2012). Detecting representations of recent and remote autobiographical memories in vmPFC and hippocampus. *J Neurosci, 32*(47), 16982-16991. doi: 10.1523/JNEUROSCI.2475-12.2012

Burgess, P. W., Dumontheil, I., & Gilbert, S. J. (2007). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends Cogn Sci, 11*(7), 290-298. doi: 10.1016/j.tics.2007.05.004

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: a neural model of spatial memory and imagery. *Psychol Rev, 114*(2), 340-375. doi: 10.1037/0033-295X.114.2.340

Calarge, C., Andreasen, N. C., & O'Leary, D. S. (2003). Visualizing how one brain understands another: a PET study of theory of mind. *Am J Psychiatry, 160*(11), 1954-1964.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*(Pt 3), 564-583. doi: 10.1093/brain/awl004

Chapman, S., Colvin, L. E., Vuorre, M., Cocchini, G., Metcalfe, J., Huey, E. D., & Cosentino, S. (2018). Cross domain self-monitoring in anosognosia for memory loss in Alzheimer's disease. *Cortex, 101*, 221-233. doi: 10.1016/j.cortex.2018.01.019

Chavoix, C., & Insausti, R. (2017). Self-awareness and the medial temporal lobe in neurodegenerative diseases. *Neurosci Biobehav Rev, 78*, 1-12. doi: 10.1016/j.neubiorev.2017.04.015

Clare, L., Markova, I. S., Roth, I., & Morris, R. G. (2011). Awareness in Alzheimer's disease and associated dementias: theoretical framework and clinical implications. *Aging Ment Health, 15*(8), 936-944. doi: 10.1080/13607863.2011.583630

Clare, L., Wilson, B. A., Carter, G., Breen, K., Gosses, A., & Hodges, J. R. (2000). Intervening with everyday memory problems in dementia of Alzheimer type: an errorless learning approach. *J Clin Exp Neuropsychol, 22*(1), 132-146. doi: 10.1076/1380-3395(200002)22:1;1-8;FT132

Conway, M. A. (2009). Episodic memories. *Neuropsychologia, 47*(11), 2305-2313.

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol Rev, 107*(2), 261-288.

Conway, M. A., Singer, J. A., & Tagini, A. (2004). The self and autobiographical memory: correspondence and coherence. *Social Cognition, 22*(5), 491-529.

Cosentino, S., Brickman, A. M., Griffith, E., Habeck, C., Cines, S., Farrell, M., . . . Stern, Y. (2015). The right insula contributes to memory awareness in cognitively diverse older adults. *Neuropsychologia, 75*, 163-169. doi: 10.1016/j.neuropsychologia.2015.05.032

Cosentino, S., Metcalfe, J., Butterfield, B., & Stern, Y. (2007). Objective metamemory testing captures awareness of deficit in Alzheimer's disease. *Cortex, 43*(7), 1004-1019.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nat Neurosci, 7*(2), 189-195. doi: 10.1038/nn1176

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis. *Front Hum Neurosci, 7*, 372. doi: 10.3389/fnhum.2013.00372

D'Argembeau, A., Ruby, P., Collette, F., Degueldre, C., Balteau, E., Luxen, A., . . . Salmon, E. (2007). Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective-taking. *J Cogn Neurosci, 19*, 935-944.

Davey, C. G., Pujol, J., & Harrison, B. J. (2016). Mapping the self in the brain's default mode network. *Neuroimage, 132*, 390-397. doi: 10.1016/j.neuroimage.2016.02.022

Dodson, C. S., Spaniol, M., O'Connor, M. K., Deason, R. G., Ally, B. A., & Budson, A. E. (2011). Alzheimer's disease and memory-monitoring impairment: Alzheimer's patients show a monitoring deficit that is greater than their accuracy deficit. *Neuropsychologia, 49*(9), 2609-2618. doi: 10.1016/j.neuropsychologia.2011.05.008

Eustache, F., Piolino, P., Giffard, B., Viader, F., De La Sayette, V., Baron, J. C., & Desgranges, B. (2004). 'In the course of time': a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer's disease. *Brain, 127*(Pt 7), 1549-1560.

Farb, N. A., Segal, Z. V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc Cogn Affect Neurosci, 2*(4), 313-322. doi: 10.1093/scan/nsm030

Farrell, M. J., & Robertson, I. H. (1998). Mental rotation and automatic updating of body-centered spatial relationships. *J. Exp. Psychol. Learn. Mem. Cogn., 24*, 227. doi: doi:10.1037/0278-7393.24.1.227

Finn, B. (2017). A framework of episodic updating: An account of memory updating after retrieval. In B. H. Ross (Ed.), *The Psychology of Learning and Motivation* (pp. 173-211): Elsevier Academic Press.

Fleming, S. M., & Dolan, R. J. (2012). The neural basis of metacognitive ability. *Philos Trans R Soc Lond B Biol Sci, 367*(1594), 1338-1349. doi: 10.1098/rstb.2011.0417

Frewen, P., Schroeter, M. L., Riva, G., Cipresso, P., Fairfield, B., Padulo, C., . . . Northoff, G. (2020). Neuroimaging the consciousness of self: Review, and conceptual-methodological framework. *Neurosci Biobehav Rev, 112*, 164-212. doi: 10.1016/j.neubiorev.2020.01.023

Gallo, D. A., Chen, J. M., Wiseman, A. L., Schacter, D. L., & Budson, A. E. (2007). Retrieval monitoring and anosognosia in Alzheimer's disease. *Neuropsychology, 21*(5), 559-568.

Garland, M. M., Vaidya, J. G., Tranel, D., Watson, D., & Feinstein, J. S. (2021). Who Are You? The Study of Personality in Patients With Anterograde Amnesia. *Psychol Sci, 32*(10), 1649-1661. doi: 10.1177/09567976211007463

Genon, S., Bahri, M. A., Collette, F., Angel, L., d'Argembeau, A., Clarys, D., . . . Bastin, C. (2014). Cognitive and neuroimaging evidence of impaired interaction between self and memory in Alzheimer's disease. *Cortex, 51*, 11-24. doi: 10.1016/j.cortex.2013.06.009

Genon, S., Collette, F., Feyers, D., Phillips, C., Salmon, E., & Bastin, C. (2013). Item familiarity and controlled associative retrieval in Alzheimer's disease: an fMRI study. *Cortex, 49*(6), 1566-1584. doi: 10.1016/j.cortex.2012.11.017

Genon, S., Simon, J., Bahri, M. A., Collette, F., Souchay, C., Jaspar, M., . . . Salmon, E. (2016). Relating pessimistic memory predictions to Alzheimer's disease brain structure. *Cortex, 85*, 151-164. doi: 10.1016/j.cortex.2016.09.014

Geurten, M., Salmon, E., & Bastin, C. (2021). Impaired explicit self-awareness but preserved behavioral regulation in patients with Alzheimer disease. *Aging Ment Health, 25*(1), 142-148. doi: 10.1080/13607863.2019.1675142

Gil, R., Arroyo-Anllo, E. M., Ingrand, P., Gil, M., Neau, J. P., Ornon, C., & Bonnaud, V. (2001). Self-consciousness and Alzheimer's disease. *Acta Neurol Scand, 104*(5), 296-300.

Gomez, A., Cerles, M., Rousset, S., Remy, C., & Baciu, M. (2014). Differential hippocampal and retrosplenial involvement in egocentric-updating, rotation, and allocentric processing during online spatial encoding: an fMRI study. *Front Hum Neurosci, 8*, 150. doi: 10.3389/fnhum.2014.00150

Gray, J. (1995). The contents of consciousness: a neuropsychological conjecture. *Behavioral and brain Sciences, 18*, 659-722.

Grewal, R. P. (1994). Self-recognition in dementia of the Alzheimer type. *Percept Mot Skills, 79*(2), 1009-1010.

Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. *J Comp Neurol, 521*(15), 3371-3388. doi: 10.1002/cne.23368

Guerrier, L., Le Men, J., Gane, A., Planton, M., Salabert, A. S., Payoux, P., . . . Pariente, J. (2018). Involvement of the Cingulate Cortex in Anosognosia: A Multimodal Neuroimaging Study in Alzheimer's Disease Patients. *J Alzheimers Dis, 65*(2), 443-453. doi: 10.3233/JAD-180324

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A, 98*(7), 4259-4264.

Hallam, B., Chan, J., Gonzalez Costafreda, S., Bhome, R., & Huntley, J. (2020). What are the neural correlates of meta-cognition and anosognosia in Alzheimer's disease? A systematic review. *Neurobiol Aging, 94*, 250-264. doi: 10.1016/j.neurobiolaging.2020.06.011

Jedidi, H., Feyers, D., Collette, F., Bahri, M. A., Jaspar, M., d'Argembeau, A., . . . Bastin, C. (2013). Dorsomedial prefrontal metabolism and unawareness of current characteristics of personality traits in Alzheimer's disease. *Soc Cogn Affect Neurosci*. doi: 10.1093/scan/nst132

Jiang, S., Wang, S., & Wan, X. (2022). Metacognition and mentalizing are associated with distinct neural representations of decision uncertainty. *PLoS Biol, 20*(5), e3001301. doi: 10.1371/journal.pbio.3001301

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., . . . Herholz, K. (2005). Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. *Dement Geriatr Cogn Disord, 19*(5-6), 349-356.

Kim, H. (2020). Stability or Plasticity? - A Hierarchical Allostatic Regulation Model of Medial Prefrontal Cortex Function for Social Valuation. *Front Neurosci, 14*, 281. doi: 10.3389/fnins.2020.00281

Kircher, T. T., Senior, C., Phillips, M. L., Benson, P. J., Bullmore, E. T., Brammer, M., . . . David, A. S. (2000). Towards a functional neuroanatomy of self processing: effects of faces and words. *Brain Res Cogn Brain Res, 10*(1-2), 133-144.

Klein, S. B., Cosmides, L., & Costabile, K. A. (2003). Preserved knowledge of self in a case of Alzheimer's dementia. *Soc Cogn, 21*(2), 157-165.

Klein, S. B., & Gangi, C. E. (2010). The multiplicity of self: neuropsychological evidence and its implications for the self as a construct in psychological research. *Ann N Y Acad Sci, 1191*, 1-15. doi: 10.1111/j.1749-6632.2010.05441.x

Klein, S. B., Loftus, J., & Kihlstrom, J. F. (1996). Self-knowledge of an amnesic patient: toward a neuropsychology of personality and social psychology. *J Exp Psychol Gen, 125*(3), 250-260.

Klein, S. B., Rozendal, K., & Cosmides, L. (2002). A social-cognitive neuroscience analysis of the self. *Soc Cogn, 20*(2), 105-135.

Knyazev, G. G., Savostyanov, A. N., Bocharov, A. V., Levin, E. A., & Rudych, P. D. (2020). Intrinsic Connectivity Networks in the Self- and Other-Referential Processing. *Front Hum Neurosci, 14*, 579703. doi: 10.3389/fnhum.2020.579703

Lattanzio, L., Seames, A., Holden, S. K., & Buard, I. (2021). The emergent relationship between temporoparietal junction and anosognosia in Alzheimer's disease. *J Neurosci Res, 99*(9), 2091-2096. doi: 10.1002/jnr.24904

Lenzoni, S., Morris, R. G., & Mograbi, D. C. (2020). The Petrified Self 10 Years After: Current Evidence for Mnemonic anosognosia. *Front Psychol, 11*, 465. doi: 10.3389/fpsyg.2020.00465

Lewis, M. (2011). The origins and uses of self-awarenesss or the mental representation of me. *Conscious Cogn, 20*(1), 120-129.

Marcel, A. J., Tegner, R., & Nimmo-Smith, I. (2004). Anosognosia for plegia: specificity, extension, partiality and disunity of bodily unawareness. *Cortex, 40*(1), 19-40.

Markowitsch, H. J., & Staniloiu, A. (2011). Memory, autonoetic consciousness, and the self. *Conscious Cogn, 20*(1), 16-39.

Massimo, L., Libon, D. J., Chandrasekaran, K., Dreyfuss, M., McMillan, C. T., Rascovsky, K., . . . Grossman, M. (2013). Self-appraisal in behavioural variant frontotemporal degeneration. *J Neurol Neurosurg Psychiatry, 84*(2), 148-153. doi: 10.1136/jnnp-2012-303153

McCaig, R. G., Dixon, M., Keramatian, K., Liu, I., & Christoff, K. (2011). Improved modulation of rostrolateral prefrontal cortex using real-time fMRI training and meta-cognitive awareness. *Neuroimage, 55*(3), 1298-1305. doi: 10.1016/j.neuroimage.2010.12.016

McDermott, K. B., Szpunar, K. K., & Christ, S. E. (2009). Laboratory-based and autobiographical retrieval tasks differ substantially in their neural substrates. *Neuropsychologia, 47*(11), 2290-2298. doi: 10.1016/j.neuropsychologia.2008.12.025

Meulenbroek, O., Rijpkema, M., Kessels, R. P., Rikkert, M. G., & Fernandez, G. (2010). Autobiographical memory retrieval in patients with Alzheimer's disease. *Neuroimage, 53*(1), 331-340. doi: 10.1016/j.neuroimage.2010.05.082

Mimura, M., & Yano, M. (2006). Memory impairment and awareness of memory deficits in early-stage Alzheimer's disease. *Rev Neurosci, 17*(1-2), 253-266.

Mitchell, J. P. (2008). Activity in right temporo-parietal junction is not selective for theory-of-mind. *Cereb Cortex, 18*(2), 262-271.

Mitchell, J. P., Macrae, C. N., & Banaji, M. R. (2004). Encoding-specific effects of social cognition on the neural correlates of subsequent memory. *J Neurosci, 24*(21), 4912-4917.

Mograbi, D. C., Brown, R. G., & Morris, R. G. (2009). Anosognosia in Alzheimer's disease--the petrified self. *Conscious Cogn, 18*(4), 989-1003.

Mograbi, D. C., Huntley, J., & Critchley, H. (2021). Self-awareness in Dementia: a Taxonomy of Processes, Overview of Findings, and Integrative Framework. *Curr Neurol Neurosci Rep, 21*(12), 69. doi: 10.1007/s11910-021-01155-6

Mograbi, D. C., & Morris, R. G. (2013). Implicit awareness in anosognosia: clinical observations, experimental evidence, and theoretical implications. *Cogn Neurosci, 4*(3-4), 181-197. doi: 10.1080/17588928.2013.833899

Molenberghs, P., Johnson, H., Henry, J. D., & Mattingley, J. B. (2016). Understanding the minds of others: A neuroimaging meta-analysis. *Neurosci Biobehav Rev, 65*, 276-291. doi: 10.1016/j.neubiorev.2016.03.020

Mondragon, J. D., Maurits, N. M., & De Deyn, P. P. (2019). Functional Neural Correlates of Anosognosia in Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review. *Neuropsychol Rev, 29*(2), 139-165. doi: 10.1007/s11065-019-09410-x

Morales, J., Lau, H., & Fleming, S. M. (2018). Domain-General and Domain-Specific Patterns of Activity Supporting Metacognition in Human Prefrontal Cortex. *J Neurosci, 38*(14), 3534-3546. doi: 10.1523/JNEUROSCI.2360-17.2018

Moran, J. M., Kelley, W. M., & Heatherton, T. F. (2013). What Can the Organization of the Brain's Default Mode Network Tell us About Self-Knowledge? *Front Hum Neurosci, 7*, 391. doi: 10.3389/fnhum.2013.00391

Morganti, F., Stefanini, S., & Riva, G. (2013). From allo- to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cogn Neurosci, 4*(3-4), 171-180. doi: 10.1080/17588928.2013.854762

Morris, R. G., & Hannesdottir, K. (2004). Loss of "awareness" in Alzheimer's disease. In R. G. Morris & J. T. Becker (Eds.), *Cognitive Neuropsychology of Alzheimer's Disease* (pp. 275–296). Oxford: Oxford University Press.

Morris, R. G., & Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex, 49*(6), 1553-1565. doi: 10.1016/j.cortex.2012.09.006

Moscovitch, M., & Winocur, G. (1992). The Neuropsychology of Memory and Aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (pp. 315-372). Hillsdale, NJ: Erlbaum.

Moulin, C. J. A., Perfect, T., & Jones, R. W. (2000). Global predictions of memory in Alzheimer's disease: Evidence for preserved metamemory monitoring. *Aging, Neuropsychology and Cognition, 7*, 230-244.

Nelson, T. O., & Narens, L. (1990). Metamemory: A theoretical framework and some new findings. In G. H. Bower (Ed.), *The Psychology of Learning and Motivation* (Vol. 26, pp. 125-173). New York: Academic Press.

Nobili, F., Mazzei, D., Dessi, B., Morbelli, S., Brugnolo, A., Barbieri, P., . . . Pagani, M. (2010). Unawareness of memory deficit in amnestic MCI: FDG-PET findings. *J Alzheimers Dis.*, *22*(3), 993-1003.

Northoff, G., Qin, P., & Feinberg, T. E. (2011). Brain imaging of the self--conceptual, anatomical and methodological issues. *Conscious Cogn, 20*(1), 52-63.

Ochsner, K. N., Beer, J. S., Robertson, E. R., Cooper, J. C., Gabrieli, J. D., Kihsltrom, J. F., & D'Esposito, M. (2005). The neural correlates of direct and reflected self-knowledge. *Neuroimage, 28*(4), 797-814.

Perrotin, A., Desgranges, B., Landeau, B., Mezenge, F., La Joie, R., Egret, S., . . . Chetelat, G. (2015). Anosognosia in Alzheimer disease: Disconnection between memory and self-related brain networks. *Ann Neurol, 78*(3), 477-486. doi: 10.1002/ana.24462

Philippi, N., Noblet, V., Botzung, A., Despres, O., Renard, F., Sfikas, G., . . . Blanc, F. (2012). MRI-based volumetry correlates of autobiographical memory in Alzheimer's disease. *PLoS One, 7*(10), e46200. doi: 10.1371/journal.pone.0046200

Piolino, P. (2003). [Autobiographical memory in aging]. *Psychol Neuropsychiatr Vieil, 1*(1), 25-35.

Piolino, P., Desgranges, B., Belliard, S., Matuszewski, V., Lalevee, C., De la Sayette, V., & Eustache, F. (2003). Autobiographical memory and autonoetic consciousness: triple dissociation in neurodegenerative diseases. *Brain, 126*(Pt 10), 2203-2219.

Piolino, P., Desgranges, B., & Eustache, F. (2009). Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia, 47*(11), 2314-2329.

Prebble, S. C., Addis, D. R., & Tippett, L. J. (2013). Autobiographical memory and sense of self. *Psychol Bull, 139*(4), 815-840. doi: 10.1037/a0030146

Prigatano, G. P. (2009). Anosognosia: clinical and ethical considerations. *Curr Opin Neurol, 22*(6), 606-611.

Qiu, L., Su, J., Ni, Y., Bai, Y., Zhang, X., Li, X., & Wan, X. (2018). The neural system of metacognition accompanying decision-making in the prefrontal cortex. *PLoS Biol, 16*(4), e2004037. doi: 10.1371/journal.pbio.2004037

Razafimahatratra, S., Guieysse, T., Lejeune, F. X., Houot, M., Medani, T., Dreyfus, G., . . . Andrade, K. (2023). Can a failure in the error-monitoring system explain unawareness of memory deficits in Alzheimer's disease? *Cortex*. doi: 10.1016/j.cortex.2023.05.014

Renoult, L., Irish, M., Moscovitch, M., & Rugg, M. D. (2019). From Knowing to Remembering: The Semantic-Episodic Distinction. *Trends Cogn Sci, 23*(12), 1041-1057. doi: 10.1016/j.tics.2019.09.008

Ries, M. L., Jabbar, B. M., Schmitz, T. W., Trivedi, M. A., Gleason, C. E., Carlsson, C. M., . . . Johnson, S. C. (2007). Anosognosia in mild cognitive impairment: Relationship to activation of cortical midline structures involved in self-appraisal. *J Int Neuropsychol Soc, 13*(3), 450-461. doi: 10.1017/S1355617707070488

Rosen, H. J. (2011). Anosognosia in neurodegenerative disease. *Neurocase, 17*(3), 231-241. doi: 10.1080/13554794.2010.522588

Rosen, H. J., Alcantar, O., Rothlind, J., Sturm, V., Kramer, J. H., Weiner, M., & Miller, B. L. (2010). Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease. *Neuroimage, 49*(4), 3358-3364.

Ruby, P., Collette, F., D'Argembeau, A., Peters, F., Degueldre, C., Balteau, E., . . . Salmon, E. (2009). Perspective taking to assess self-personality: what's modified in Alzheimer's disease? *Neurobiol Aging, 30*(10), 1637-1651.

Ruby, P., & Decety, J. (2004). How Would You Feel versus How Do You Think She Would Feel? A Neuroimaging Study of Perspective-Taking with Social Emotions. *J Cogn Neurosci, 16*(6), 988-999.

Ruby, P., Schmidt, C., Hogge, M., D'Argembeau, A., Collette, F., & Salmon, E. (2007). Social mind representation: where does it fail in frontotemporal dementia? *J Cogn Neurosci, 19*(4), 671-683.

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., . . . Garraux, G. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp, 27*(7), 588-597.

Samson, D., Apperly, I. A., Chiavarino, C., & Humphreys, G. W. (2004). Left temporoparietal junction is necessary for representing someone else's belief. *Nat Neurosci, 7*(5), 499-500.

Schaefer, A., Collette, F., Philippot, P., van der Linden, M., Laureys, S., Delfiore, G., . . . Salmon, E. (2003). Neural correlates of "hot" and "cold" emotional processing: a multilevel approach to the functional anatomy of emotion. *Neuroimage, 18*(4), 938-949.

Schilbach, L., Eickhoff, S. B., Rotarska-Jagiela, A., Fink, G. R., & Vogeley, K. (2008). Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. *Conscious Cogn, 17*(2), 457-467.

Seow, T. X. F., Rouault, M., Gillan, C. M., & Fleming, S. M. (2021). How Local and Global Metacognition Shape Mental Health. *Biol Psychiatry, 90*(7), 436-446. doi: 10.1016/j.biopsych.2021.05.013

Serino, S., Cipresso, P., Morganti, F., & Riva, G. (2014). The role of egocentric and allocentric abilities in Alzheimer's disease: a systematic review. *Ageing Res Rev, 16*, 32-44. doi: 10.1016/j.arr.2014.04.004

Serino, S., & Riva, G. (2017). The Proactive Self in Space: How Egocentric and Allocentric Spatial Impairments Contribute to Anosognosia in Alzheimer's Disease. *J Alzheimers Dis, 55*(3), 881-892. doi: 10.3233/JAD-160676

Silva, A. R., Pinho, M. S., Macedo, L., Souchay, C., & Moulin, C. (2017). Mnemonic anosognosia in Alzheimer's disease is caused by a failure to transfer online evaluations of performance: Evidence from memory training programs. *J Clin Exp Neuropsychol, 39*(5), 419-433. doi: 10.1080/13803395.2016.1231799

Souchay, C. (2007). Metamemory in Alzheimer's disease. *Cortex, 43*(7), 987-1003. doi: 10.1016/s0010-9452(08)70696-8

St Jacques, P. L., Olm, C., & Schacter, D. L. (2013). Neural mechanisms of reactivation-induced updating that enhance and distort memory. *Proc Natl Acad Sci U S A, 110*(49), 19671-19678. doi: 10.1073/pnas.1319630110

Strikwerda-Brown, C., Grilli, M. D., Andrews-Hanna, J., & Irish, M. (2019). "All is not lost"-Rethinking the nature of memory and the self in dementia. *Ageing Res Rev, 54*, 100932. doi: 10.1016/j.arr.2019.100932

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia, 44*(12), 2189-2208.

Tacikowski, P., Berger, C. C., & Ehrsson, H. H. (2017). Dissociating the Neural Basis of Conceptual Self-Awareness from Perceptual Awareness and Unaware Self-Processing. *Cereb Cortex, 27*(7), 3768-3781. doi: 10.1093/cercor/bhx004

Tulving, E. (1985). Memory and Consciousness. *Canadian Psychologist, 25*, 1-12.

Vaccaro, A. G., & Fleming, S. M. (2018). Thinking about thinking: A coordinate-based meta-analysis of neuroimaging studies of metacognitive judgements. *Brain Neurosci Adv, 2*, 2398212818810591. doi: 10.1177/2398212818810591

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Hum Brain Mapp, 30*, 829-858.

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., . . . Sperling, R. A. (2017). Anosognosia for memory deficits in mild cognitive impairment: Insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin, 15*, 408-414. doi: 10.1016/j.nicl.2017.05.020

Vinogradova, O. S. (2001). Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus, 11*(5), 578-598.

Vogel, A., Hasselbalch, S. G., Gade, A., Ziebell, M., & Waldemar, G. (2005). Cognitive and functional neuroimaging correlate for anosognosia in mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry, 20*(3), 238-246.

Walter, M., Matthia, C., Wiebking, C., Rotte, M., Tempelmann, C., Bogerts, B., . . . Northoff, G. (2009). Preceding attention and the dorsomedial prefrontal cortex: process specificity versus domain dependence. *Hum Brain Mapp, 30*(1), 312-326. doi: 10.1002/hbm.20506

Wilson, T. D., & Dunn, E. W. (2004). Self-knowledge: its limits, value, and potential for improvement. *Annu Rev Psychol, 55*, 493-518.

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., . . . Wilcock, G. K. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex, 49*(3), 668-678. doi: 10.1016/j.cortex.2012.04.011

Zamboni, G., Grafman, J., Krueger, F., Knutson, K. M., & Huey, E. D. (2010). Anosognosia for behavioral disturbances in frontotemporal dementia and corticobasal syndrome: A

voxel-based morphometry study. *Dement Geriatr Cogn Disord, 29*(1), 88-96. doi: 10.1159/000255141