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Review article

Self, cortical midline structures and the resting state: Implications for Alzheimer's disease

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ABSTRACT

Different aspects of the self have been reported to be affected in many neurological or psychiatric diseases such as Alzheimer's disease (AD), including mainly higher-level cognitive self-unawareness. This higher sense of self-awareness is most likely related to and dependent on episodic memory, due to the proper integration of ourselves in time, with a permanent conservation of ourselves (*i.e.*, sense of continuity across time). Reviewing studies in this field, our objective is thus to raise possible explanations, especially with the help of neuroimaging studies, for where such self-awareness deficits originate in AD patients. We describe not only episodic (and autobiographical memory) impairment in patients, but also the important role of cortical midline structures, the Default Mode Network, and the resting state (intrinsic brain activity) for the processing of self-related information.

Contents

1. The self

Understanding the concept of self is a challenge for philosophers and scientists. Defining the self is an issue that humans have faced long before the emergence of psychology. Although the literature includes countless articles, chapters, and books that try to build a suitable concept, there is no coherent body of knowledge that comprises a cognitive explanation of the self. Phylogenetically speaking, a more primordial concept of self has been raised to define the relationship between the organisms with the environment (Panksepp and Northoff, 2009), that is, the biological urges that make them active creatures reacting to their interoceptive goals towards the world's exteroceptive stimuli. This so-called 'core self' is believed to be present among all mammals and was postulated to be a basic neural function composed of viscero-somatic and subcortical structures that, although initially aimless, promoted a higher aspect of

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self-related process (Northoff and Panksepp, 2008). This 'core self', or 'minimal self', is the most basic level of the self and refers to the consciousness of oneself as an immediate subject of experience that is temporally and spatially confined to the immediate present (Clare et al., 2011); this self does not require language nor working memory but only a short-term memory (Damasio, 1998). It has a relationship with time processing in the sense that perceptions and actions should be continually sensed by someone; disruptions in this system (and therefore in the 'minimal self') are commonly seen in schizophrenic patients (Martin et al., 2014).

The 'reflexive self', on the other hand, is intentionally directed towards the act of consciousness itself, such as someone thinking of perceiving something and being the object of awareness (*i.e.*, self-referential). The distinction between self-related and self-referential processing (see also (Northoff et al., 2006)) can also be conceived as the line that demarcates or differentiates the human self from other animals. Beyond the perception that something is happening to us, humans can also reflect upon the perception that something is happening to us (Mograbi et al., 2009). We are the object of our own attention, we are aware of our existence, and we are aware of being aware. We judge thoughts and actions and identify one's own abilities, attitudes, and behaviors, recalling our own experience to assume the existence of comparable experience in others. Due to the capacity of mirror-recognition, chimpanzees and orangutans were claimed to have an extended self, for which a certain kind of subcortical networking was enough for this process (Northoff and Panksepp, 2008); however, recalling from our own experience a sequence of specific events in time and place might be a uniquely human feature (Levine, 2004).

This higher sense of self-awareness might be related to and dependent on episodic memory (Fargeau et al., 2010), as every day we have the feeling of being the same person because we remember who we are now and were before. By the proper integration of ourselves in time, we know we are the same person today we were in the past and will be in the future, and therefore we have a permanent conservation of ourselves. The term 'autonoesis' (Tulving, 2002) refers to self-knowing and has been used to refer to this type of consciousness that allows us to be aware of subjective time in which events happened. This has also been called the 'autobiographical self' by Damasio (1998); it describes the human capacity of representing ourselves mentally in time and becoming aware of this representation and linking personal experiences with self through consciously recalling. Personal memories help establish personal identity (D'Argembeau et al., 2014) through the knowledge of ourselves, which in turn emerges from our life history and experiences. How we represent ourselves in our mind creates a sense of identity, which in turn can be broken into self-knowledge (*e.g.*, knowledge of our own traits) and narratives (*e.g.*, our life, experiences, personal history) (Addis and Tippett, 2004).

Clare et al. (2011) have proposed a model in which the self is composed of four different aspects: sensory registration, performance monitoring, evaluative judgment, and meta-representation. Whereas the first aspect involves only simple internal representations ('core self'), the other three require capacities that are more complex. For instance, performance monitoring includes monitoring ongoing task performance and identifying errors; evaluative judgment refers to the individual's awareness of their abilities, symptoms, or situation; and meta-representation refers to the ability to consider the perspective of others or other situations (Clare et al., 2011). Klein et al. (2003) have mentioned at least five isolable components for the unified self: episodic memories of one's own life, representations of one's own personality traits, facts about one's personal history (semantic personal knowledge), experience of personal agency and continuity through time, and the ability to reflect on one's own thoughts and experiences.

That said, now imagine a situation where you do not have access to your own life history, and there is no continuity. All your brain has access to is some broken pieces of information, sometimes antique, that may not make sense as a narrative personal history. You do not remember what you did yesterday or even how you felt. It is like reading a book with missing or repeated chapters, which makes it difficult to follow and understand. This is probably the situation that some Alzheimer's disease (AD) patients face. AD patients lose self-awareness in several aspects that involve complex cognitive abilities and allow them to know who they are. Reviewing studies in this field, our objective is thus to raise possible explanations, especially with the help of neuroimaging studies, to determine where such self-awareness deficits originate. We shall begin with a phenomenological approach regarding AD phenotype and describe the aspects of the self that have been reported to be altered in these patients. We highlight the importance of self-continuity across time; then, we bring neuroimaging findings to support and fit an existing model to AD.

2. Alzheimer's disease and impairments of the self

Different aspects of the self have been reported to be affected in many neurological or psychiatric diseases, such as dementia, although there is no doubt that some aspects of the self might still be present in AD patients even with moderate impairment. Due to the occurrence of moments of clarity following periods of confusion, it can be hard for the family and caregivers to understand how much awareness the patients still maintain (Clare and Woods, 2005). Regarding the sensory registration level raised by Clare et al. (2011), for example, some studies have demonstrated that advanced patients who are still able to verbally communicate respond to discomfort, pain, noise, or change of temperature (Clare et al., 2008). Also, AD patients express a range of affective signals and present an intact and functional emotion system even in the advanced stages (Magai et al., 1996). The awareness of existing is also preserved among AD patients (Gil et al., 2001).

Visual self-recognition in photographs and mirrors were also objects of study in the AD field. Although mild patients still present preserved visual self-recognition in photographs (even though they have no memory of the photographic session) (Fazio and Mitchell, 2009), this scenario can change in more advanced phases. Some patients, for example, can misidentify their own reflection in the mirror in later stages. Breen et al. (2001) described two patients who were unable to recognize their own reflection and attempted to communicate with the reflected person. One patient believed that his own reflection was another person who was following him around and who could be seen anywhere that there was a reflecting surface. While attempting to communicate with the reflected person on numerous occasions without success, he was somewhat perturbed that the person never replied. The second patient said that as the person never replied he could only assume that there was something wrong with himself.

Perhaps the most reported aspect of the self to be impaired in AD is the memory/cognitive impairment awareness, also called anosognosia. Anosognosia refers to the impaired judgment of AD patients of their own cognitive deficit, behavior, or daily activities and may be assessed by the discrepant score between the subject's evaluation and the evaluation of someone close to them. Even in the earlier stages, AD patients present unawareness to recognize their cognitive impairment and medical condition (Clare et al., 2012; Zamboni et al., 2013), have the tendency to overestimate their ability to consider perceptions (Degirmenci et al., 2013), and present impairment in judging the level of success or failure on daily tasks (Morris and Mograbi, 2013). Anosognosia symptoms also tend to worsen with disease severity (Gil et al., 2001).

Anosognosia is a higher-level process because it includes judgments, attributions, and reflection. Salmon et al. (2005) interpreted it as an impairment to see oneself through a third person perspective, and Agnew and Morris (1998) related it to a failure to update the self-awareness system in relation to those of others. It can be related to memory in the sense that the subject should compare the current memory functioning with their past memory functioning (Clare et al., 2011); however, Hannesdottir and Morris (Hannesdottir and Morris, 2007) proposed a neuropsychological model to distinguish anosognosia secondary to memory/executive dysfunction from primary anosognosia (which instead is caused by a break in the long-term and self-awareness system itself). We will come back to this issue later in the text. Some studies (Maki et al., 2012) have used the term 'impaired self-awareness' to refer to anosognosia specifically; therefore, in a simplistic way, impaired self-awareness in AD goes beyond cognitive self-evaluation.

In clinical settings and among their families, for example, caregivers and close ones often report that AD patients are no longer themselves and display behaviors from past self-identities. For example, a woman with severe dementia presented retrievable knowledge of her personality traits and those of her daughter, but the knowledge of her personality was from before the onset of the disease (Klein et al., 2003). The authors also report a deep change in the patient's personality as the disease progressed, although the patient was unaware of this transformation. In addition, some AD patients are often said to be absent-minded and disconnected from the present (Globerman, 1995); whereas for others there could be only the immediate present and the long-ago past (Huddleston, 2010). They lose strength, quality and direction of identity and individuality (Addis and Tippett, 2004), and as the disease progresses, they also lose the ability to define themselves as they once did (Basting, 2003).

Regarding trait adjectives of self-knowledge, in which participants are required to describe their own personality (*e.g.*, "are you patient?") or the personality of a close friend (*e.g.*, "is John patient?"), results are interesting. One study found that AD patients presented less accurate self-representations than healthy older adults (both when making the judgments from their own perspective and from the perspective of their relatives) (Ruby et al., 2009). Also, another study found that demented patients had worse performance only when they were asked to judge themselves but not when evaluating a close person (Zamboni et al., 2013). Studies involving this kind of methodology, in which patients are asked to evaluate self adjectives either from their point of view or from someone else's, allow us to investigate the meta-representational level of awareness presented in AD patients. When participants are required to answer such questions, they should be able to self-transport to another point of view (projecting into this new perspective) and make judgments about themselves.

Meta-representation, however, is not restricted to the ability of seeing oneself from a third person perspective specifically. Being able to watch oneself from another point in time is a process that also requires a new perspective view. For example, in a functional MRI study (fMRI) (D'Argembeau et al., 2008), participants were instructed to reflect on their own traits and those of a close other for both their present life period and a past life period. The authors found that thinking about the past self and thinking about the other person were associated with similar levels of activity in the same brain areas. Interestingly, the effect of temporal distance was symmetrical between the past and the future events (D'Argembeau et al., 2010). This process of recollecting past events, also called autobiographical memory (ABM), will now be described due to its importance in AD.

3. Autobiographical memory: the feeling of being continuous in time

Recollection of ABMs has been likened to mentally traveling back in time and re-experiencing one's past, a phenomena that requires a subject to travel (for instance, 'the self') (Tulving, 2002). Time travelling, in this sense, means the ability to escape the influence of the current mental state or the ability to maintain different mental states simultaneously. It has also been called episodic future thinking (Atance, 2005), memory for the future (Ingvar, 1985), pre-experiencing (D'Argembeau and Van der Linden, 2004), and imagination (Decety and Grezes, 2006). Such a process requires the involvement of a high order cognitive ability named meta-representation (or self-projection (Buckner and Carroll, 2007), sense of subjective time (Tulving, 2002), and self from the inside (Suddendorf and Corballis, 1997)), in which the subject shifts from the perspective of the immediate present to alternative perspectives, such as the past or the imagined future.

It seems important to clarify and differentiate the definition of 'autobiographical memory', 'episodic thinking', and 'mental time travel'. While mental time travel is a mental ability that involves both past and future thinking, autobiographical memory refers to projecting oneself back in time and recalling only personal past events. The episodic memory system enables conscious recollection of these past episodes (Suddendorf et al., 2009), and with regards to memories related to the self, for example, it allows oneself to re-experience them. The semantic aspect of the ABM specifically contains the knowledge and facts of our past, including knowledge of our identity, our personal characteristics, and the facts supporting awareness of personal past events. Semantic memory relies on factual general external information of the world, such as who is the president of our country. Personal semantic memory allows us to state the name and location of the school we attended, for example, or where we lived during childhood.

The episodic aspect of the ABM, on the other hand, allows us to consciously re-experience past information, such as the feelings and emotions during events. Episodic ABM grants us access to particular information that is spatially and temporally located, empowering oneself with autonoietic consciousness (Wheeler et al., 1997). Episodic memory gives rise to the notion of mental time travel, because episodic memory means the ability to reconstruct particularities of specific events that have happened to the individual, which will be the substrate for future imagining. In other words, one needs autonoietic awareness and meta-representation ability to mental time travel and mental time travelling for ABM recollection. The mental reconstruction of past events and construction of the future may be responsible for the understanding of continuity between past and future, which allow one to understand that the past and future are on the same mental dimension.

The successful access to our life history creates in oneself the sense of unity and continuity and is experienced as part of one's past. This high level of memory and consciousness, *i.e.*, autobiographic recall, relies on the self-knowing awareness or autonoietic ability and occurs in an organized way. Pieces of information such as 'what', 'when', and 'where' combine and permit one to coherently access his past, ensuring the maintenance of one's identity in an environment that frequently changes. The self and ABM depend on each other: in providing autobiographical information about our own past, episodic memories may provide the basis for personal identity; also, one may need an awareness of self in the present in order to be able to relate memory representations to experiences of one's self in the past (Suddendorf and Corballis, 1997). A failure of recollection of ABM, on the other hand, might lead us to an insecure sense of identity (Markowitsch and Staniloiu, 2013).

Interestingly, younger adults produce more details in ABM recall than older adults, and, as they get older, adults tend to recollect fewer details about happenings, locations, perceptions, and thoughts but provide a more integrative approach to the interpretation of past experiences (Levine et al., 2002). This pattern of switching from strong episodic personal recollection to a more semantic and integrated way of recollecting things that naturally happens with ageing is magnified in early stages of AD (even though semantic memory is also impaired in the early stages of this disease). This shift pattern, however, does not affect the sense of self in healthy older adults as opposed to what happens with AD patients (Martinelli et al., 2013a). Individuals with amnestic mild cognitive impairment (aMCI), who are at risk for developing AD, already present reduced specificity of ABM recall (Donix et al., 2010; Berna et al., 2012), mainly to recent life memories (Leyhe et al., 2009), and exhibit a compromised capacity to generate vivid, self-referential visual imagery and re-experience the original emotion of events (Irish et al., 2010). Also, although the semantic aspect of the ABM could still be relatively intact (Barnabe et al., 2012) or even increased (Murphy et al., 2008) in aMCI individuals, the fact that the episodic aspect of ABM is altered in these patients is much more accepted (Tramoni et al., 2012).

In severe stages of the disease when episodic and semantic memories are lost, the patients lose their expanded, autobiographical self and seem to be confined to their "core self" or "primordial self" at the same time that they lose the ability to master temporal operations and to conceive time (objective time) as homogeneous and common to every phenomenon (Damasceno, 1996). In more advanced stages of the disease, when the dissociation between object and subjectís actions is about to be dissolved, what seems to remain is the ability to judge the time of his/her own actions (for example, as "longer" or "shorter") and the feelings and emotional reactions to situations (for example, of boring waiting, expectation, unsatisfied effort or failure) similarly to what was observed by Piaget in children before one year of age (Piaget, 1952).

In recent years, an increasing number of neuroimaging studies have suggested that remembering the past and imagining the future rely on common neural processes, involving similar networks and cognitive capacities (Okuda et al., 2003; Botzung et al., 2008; Conway, 2009). Thus, it is not surprising that amnesic patients are impaired at imagining new experiences, lacking spatial coherence and richness, and result fragmented imaginative constructions (Hassabis et al., 2007). aMCI subjects also produce fewer episodic and event-specific details for both past and future events and have difficulty constructing scenarios that have never happened (Gamboz et al., 2010); the same is true for AD patients (Addis et al., 2009). Interestingly, the greater the impairment of notion of time in AD patients, the more they behave as they used to do in the past (Harrison et al., 2005), suggesting a strong role of ABMs in the formation and updating of the self and identity.

These results lead us to assume that the sense of self-continuity shrinks in degrees in AD patients – it gets smaller and smaller thus covering shorter time durations/segments – and their time construction/projection abnormally shifts towards the past. A severely impaired episodic memory domain removes the sense of personal continuity of AD patients in their daily lives (Zakzanis and Leach, 2002), which might prevent them from updating their self-knowledge and therefore lead the patients to express earlier and antique self-knowledge (Klein et al., 2003). All these findings suggest that AD patients lose the ability to time travel, and, as they became unable to form new memories, they start losing the knowledge of who they are in the present and the ability to properly project themselves into alternative situations. By doing so, such patients may assume identities associated to the poorly accessible personal information and gradually lose their narrative, autobiographical self as they lose their episodic memory.

It is believed that episodic memories phylogenetically evolved from semantic memories, appearing much later in human evolution, while other animals present only a well-developed system for semantic memory (Tulving, 2002). Questions such as 'where have we come from?', 'what are we?', 'where are we going?' require time travelling and, consequently, subjective self-awareness, a cognitive ability which emerges together with episodic memories (Atance, 2005). Due to the involvement of higher cognitive systems for consciously re-experiencing events, episodic recollection is not firmly established before the age of four (Levine, 2004). Time travelling requires a self originated from the inside, an understanding of continuity and existence across time, and an integration of past and future regardless of the present and the external environmental needs. Evolutionarily speaking, internally generated processes are extremely adaptive because they allow the organism to address unresolved problems over long periods of time (Binder et al., 1999) and increases the organism's chances of future survival by allowing the imagination of different scenarios beyond the organism's instinct. One function of episodic memories is to keep an adaptive record of recent goals, and they need to be specific enough to provide the appropriate information when assessed (Conway, 2009). By consciously imagining different scenarios, the organism is able to consider whether a particular situation could be faced or avoided if encountered (Addis et al., 2007). Whereas simple episodic memory provides us information to guide decisions, mental time travel leads us towards more restrained choices, which in the long term is advantageous (Boyer, 2008). Time travelling is a uniquely human characteristic (Suddendorf and Busby, 2003) and phylogenetically might be merged with the enlargement of more complex societies, allowing social interactions that extend beyond cooperation and kinship. The emergence of meta-representation and consequently time travelling is associated with the prominent expansion of the frontal lobes in hominid evolution rather than being exclusively dependent on medial temporal lobe structures (Wheeler et al., 1997).

The crucial role of the hippocampus in autobiographical recollection can be visualized, for instance, in a fMRI study that investigated the cerebral areas used during the recollection of episodic ABMs throughout life (Viard et al., 2007). The authors found hippocampal activation regardless of the period of time in life during the retrieval of ABMs. In addition to that, semantic dementia patients who do not present hippocampal atrophy recall recent personal incidents better than hippocampal atrophic subjects, such as AD patients (Hou et al., 2005; Irish et al., 2011). Amnestic patients, on the contrary, have deficits recalling recent past experiences and present the inability to conceive and imagine their personal future (Corkin, 2002). Given how closely imagined experiences match episodic memories, the absence of this function mediated by the hippocampus may also affect the ability to vividly re-experience the past. ABM deficits and autonoietic unawareness are among the major complaints of AD patients and could thus be related to hippocampal atrophy (Thomann et al., 2012), a well known feature of even preclinical AD patients. However, KC, a widely studied patient who suffered an accident that caused large bilateral hippocampal lesions and deep amnesia, changed his personality but was able to relearn his trait self-knowledge (Tulving, 2002; Rosenbaum et al., 2004); although he presented no autonoietic consciousness, his self-knowledge was represented abstractly (Tulving, 1993).

In this context, Conway and Pleydell-Pearce (2000) proposed a theory emphasizing the role of more abstract, semantic forms of ABMs in constructing and organizing the representation of the self – the self-memory system. The authors suggest that the role of episodic memories is to provide records of discrete events, and because these events have minimal conceptual organization, they tend to be quickly lost. In their model, the self-memory system is composed of an autobiographical knowledge base – which contains information at three different levels: general events, lifetime periods, and event-specific knowledge – and the working self (or just the self). The autobiographical knowledge is the conceptual generic schematic knowledge of the episodic memories, and the working self modulates the access to them. The event-specific knowledge, specifically, is considered to be a summary of the content of episodic memories.

Another model, proposed by Prebble et al. (2013), provides a two-by-two matrix that defines the self without overlapping with ABMs. The framework underlies subjective *versus* objective and present *versus* temporally extended aspects of self, in which all of them relate to ABMs in different ways. According to the authors, episodic memory is a precursor for the autonoetic awareness (time-dependent aspect) and self-continuity, but semantic and abstract ABMs also help establish and maintain a coherent conceptual self.

Some other studies proposed that although necessary for ABM recollection, a unified sense of self and sense of continuity go beyond personal memories, and a more complex system may be behind the process of self-awareness. Markowitsch and Welzer (2009), for example, reported that the ability to measure and evaluate time, arranging the personal events according to what occurred earlier or later, are prerequisites for ABM. The close relationship between time consciousness and self-consciousness has been reported by Wittmann (2015), in which the author describes that 'an increased awareness of oneself coincides with as increased awareness of time'. More recently, Northoff (2015) proposed that time is temporalized and is closely linked to the self as a subject in experience (*i.e.*, self-related processing, consciousness), which might be the most fundamental function of the brain, and its intrinsic activity is no longer considered a high-order feature of cognition. ABMs, in turn, which relate to the process of the self as an object (*i.e.*, self-referential processing), is a cognitive process that comes second and is built on the basic and intrinsic concept of the self (Northoff, 2015). Similarly, Caselli et al. (2009) reported that timing difficulties of AD patients are due to disruptions in different components of the internal clock and not due to higher-order cognitive impairment (*e.g.*, memory).

Regarding the sense of continuity described above, Northoff (2013) proposed a model to complement the current bidimentional view of consciousness (composed by level and content) in which the spatiotemporal continuity ('form') represents a third dimension. In his models, the 'form' allows one to put together and organize the discrete points of time and space, providing a bridge to temporospatial gaps, and, as a result, one experiences a temporal continuum between the different contents. This third level or 'form' links different discrete points in time and space by cerebral low frequency fluctuations and functional connectivity (*i.e.*, intrinsic brain activity). Thus, we could suppose that damage in the hippocampus alone may not be enough to cause self-awareness problems in AD patients. In the next sections, we shall discuss these assumptions in further detail.

4. The cortical midline regions

The self and its different components are not "located" in a single place in the brain but may instead depend on distributed neural systems that include both cortical and subcortical structures (Northoff and Panksepp, 2008). Neuroimaging studies have shown that both the experience of past and the construction of future events activate a common network that is traditionally associated with diverse forms of self-projection processes, such as time travelling (Addis et al., 2007; Botzung et al., 2008). This common network, which is an anatomical-functional unit of cortical midline structures (CMSs) (Northoff and Bermpohl, 2004), is a fundamental component in generating a model of the self (Gallagher, 2013) since it is engaged in the processing of self-referential stimuli (Northoff et al., 2006; Genon et al., 2014; Huang et al., 2014).

According to the CMS model of self monitoring, the information of recent past experiences and imagination of the future is processed in the medial temporal lobe region including the hippocampus (Addis et al., 2007; Botzung et al., 2008) and then is represented in the prefrontal cortex, which is the entrance door to the CMSs. Once there, the self-related information is processed, decisions are made under conditions of uncertainty (when multiple possible answers are available), and, together with the memory system, a feeling of rightness is provided (Gilboa, 2004). The posterior midline regions – more specifically, the posterior cingulate cortex (PCC) together with the medial prefrontal cortex (MPFC) – have an important role in the integration of these stimuli (Northoff and Bermpohl, 2004; Northoff et al., 2006). The PCC has been related to the individual's own self-beliefs and is associated with a first-person perspective (Ochsner et al., 2005), but it has also been linked to more social processes and monitoring of the environment (Qin and Northoff, 2011). The structural maturation between PCC and MPFC has been related to the development of self-related and social-cognitive functions that emerge during adolescence (Supekar et al., 2010). The posterior parietal regions, although not being part of the CMSs, work in conjunction with these regions in the sense that they act as a convergence zone that binds episodic feature ensembles within the neocortex, linking episodic memories to each other (Shimamura, 2011). These regions are responsible for the access to the full set of details associated with a particular experienced event, and patients with lesions in parietal areas have a reduced sense for re-experiencing a past event (Berryhill, 2012). The MPFC is activated during the processing of an individual's own self-beliefs (judging whether an adjective describe him, for instance) and the individual's perception of how others view them (Ochsner et al., 2005). The function of the ventral MPFC (vMPFC), specifically, might be to represent personal value or significance to self-related contents; note that here self-related contents are not restricted to external environment but also internally generated contents (D'Argembeau, 2013). The CMSs are, thus, responsible for linking internal and external stimuli and integrate these stimuli in the emotional and autobiographical context of one's own person.

The MPFC has also been associated with semantic self-knowledge and making judgments. For example, Kelley et al. (2002) found that judgments about the self lead to greater activations in these regions than judgments about others, and Denny et al. (2012) reported that the ventral portion specifically might be more related to self judgments, whereas the dorsal portion might be responsible for making judgments about others. An increased activation in the MPFC when reflecting about one's own traits (compared to the traits of others) has also been observed in several subsequent studies (Johnson et al., 2002; Gutchess et al., 2007; Jenkins et al., 2008). Regarding trait adjectives of self-knowledge, in which participants are required to describe their own personality (*e.g.*, "are you patient?") or the personality of a close friend (*e.g.*, "is John patient?"), results are interesting in AD. One study found (Ruby et al., 2009) that not only did AD patients present less accurate self-representations than healthy older adults (both when making the judgments from their own perspective and from the perspective of their relatives), but they also activated different areas when compared to control groups. For example, AD patients predominantly activated the intraparietal sulci for the self judgment, a region associated with familiarity judgment, indicating that patients use more familiarity than recollection when assessing their personality. Also, when asked to think about the other perspective, patients recruited prefrontal regions, whereas elderly controls normally activated visual associative areas; this suggests that they use more reasoning processes than visual imagery of ABM to project themselves as a third person. Another study found that demented patients had worse performance only when they were asked to judge themselves but not when asked to evaluate a close person (Zamboni et al., 2013). In addition, patients failed to recruit the MPFC when asked to make self judgments but not when evaluating others.

The CMS unit is also remarkably similar to the network involved in the retrieval of ABMs (Cabeza et al., 2004; Gilboa, 2004; Svoboda et al., 2006; Martinelli et al., 2013b) and thinking of future events (Okuda et al., 2003; Botzung et al., 2008). Damage in the MPFC, for example, leads to an inability from the individual to build events in an appropriate temporal sequence (Milner et al., 1985), which is relevant to the brain basis of self-projection and an inefficient planning of actions that require foresight (Shallice, 1982; Unterrainer and Owen, 2006). Issues and events of personal life (*i.e.*, episodic ABM) activate more regions such as the vMPFC and posterior cingulate cortex (PCC) than the retrieval of general semantic knowledge (Andrews-Hanna et al., 2010a). D'Argembeau et al. (2014) reported that when participants were asked to engage in more concrete contents, attempting to actually re-experience the events (*i.e.*, episodic ABM retrieval), CMSs and temporal regions were activated, whereas more lateralized regions were recruited when participants were required to reflect on the personal importance of their memories (*i.e.*, ABM reasoning). The vMPFC activation, in turn, was a differential between the participants who had a higher disposition to engage in self-reflection when they thought about the significance and meaning of the memories.

Although both semantic and episodic self-knowledge are usually interpreted separately, information and details about specific events can help build the beliefs about ourselves and even influence self judgments (D'Argembeau and Salmon, 2012). For example, when asking to judge personal characteristics (*e.g.*, impatience), one might remember some occasions when they were in fact impatient. This recalling of ABMs thus somehow 'feeds' and nourishes personal self knowledge, and both processes engage common self-referential mechanisms processed by the CMSs (D'Argembeau and Salmon, 2012). In line with this view, a meta-analysis of functional neuroimaging studies has revealed that CMSs are involved in processing self-referential information across multiple cognitive domains and sensory modalities (*e.g.*, the recognition of one's own body and actions, self-face recognition, and the representation of one's own traits) (Northoff et al., 2006). The CMS unit, therefore, processes and integrates mechanisms specialized for creating and refreshing the personal database, which, in turn, also needs to be updated often for self renovation (Klein et al., 2003).

The above-mentioned network that may support self-reflection about internal thoughts and feelings is thought to mediate a "default mode of brain function", or DMN. The similarity between the CMSs activation in self-related cognition and the DMN regions most probably reflect a shared neural system for default-mode self-reference (Whitfield-Gabrieli et al., 2011), which has been confirmed with neuroimaging experiments (Andrews-Hanna et al., 2010b; Qin and Northoff, 2011; Araujo et al., 2013). In addition to that, the same regions are involved during mind-wandering (Mason et al., 2007), lapses of attention in externally oriented tasks (Weissman et al., 2006), and imagining future events (Schacter et al., 2012), which are considered to be self-oriented processes or forms of spontaneous cognition.

During the last few decades, several studies in the AD field have consistently found alterations in the DMN and its regions. These findings were not coincidental. Physiopathologically speaking, AD is characterized mainly by the deposition of extracellular and insoluble β-amyloid plaques and intracellular neurofibrillary tangles composed of hyperphosphorilated tau protein (Selkoe, 2001). This deposition occurs mainly in the DMN regions: temporal areas are highly affected by the harmful effects of phospho-tau (Thal et al., 2013), whereas the PCC is among the first regions to show β-amyloid burden (Buckner et al., 2005).

Such misfolded proteins also spread to synaptically connected nonadjacent areas in a time-dependent and predictable manner. The spreading of pathology across distant regions makes the neuronal damage extend beyond regional alterations and affects parts of the brain that are somehow connected; AD is, due to this reason, commonly called "disconnection syndrome" (Cronin-Golomb, 2010; Vallet et al., 2013). Consequently, specific systems are chronologically targeted, and clinical symptoms outreach the primary phenotype (*i.e.*, memory impairment). White matter tracts that connect DMN hubs (*e.g.*, cingulum, which links the medial temporal lobe with the PCC and the MPFC, and the corpus callosum) are widely affected (Pievani et al., 2010) and correlate with cognitive performance in AD patients too (Weiler et al., 2014a). Besides being susceptible to amyloid deposition, the PCC and the precuneus also present metabolic alterations of glucose consumption in AD patients (Minoshima et al., 1997; Kuntzelmann et al., 2013). Finally, some studies have shown that gray matter atrophy in DMN areas is associated with a poorer ABM performance (Irish et al., 2014a; Tomadesso et al., 2015); since atrophy in temporal and posterior areas is a neuroimaging signature of AD, these findings could also be observed in demented patients (Irish et al., 2014b).

Studies using functional MRI have shown that demented patients present less activation in temporal areas (Machulda et al., 2003; Sperling et al., 2003; Dickerson et al., 2005) and deactivation in the DMN (Pihlajamaki et al., 2009; Rami et al., 2012) during cognitive tasks than cognitively normal elderly. During the resting state, DMN regions show diminished connectivity (Agosta et al., 2012), which correlates with a worse performance in episodic memory tests in AD patients (Weiler et al., 2014b) and also in aMCI subjects (Sorg et al., 2007), as well as decreased amplitude of low frequency fluctuations (Weiler et al., 2014b). Higher deposition of β-amyloid corresponds to the greatest alterations in DMN connectivity, even in cognitively normal elderly who present high burden of β-amyloid, and it is assumed that the effects of altered proteins are apparent in the initial years of AD or even decades before the onset of the disease (Sheline et al., 2010; Kikuchi et al., 2011). The connectivity of the DMN, in turn, follows AD severity and continues to decline as the disease progresses (Damoiseaux et al., 2012). Moreover, the miscommunication among the DMN nodes occurs regardless of cortical damage (Gili et al., 2011; Petrella et al., 2011), suggesting that functional deficits within the network may precede structural alterations. Graph theoretical analysis also brings a loss of both structural and functional connectivity in DMN regions (Supekar et al., 2008; Tijms et al., 2013), specially an increased average characteristic path length (as a result of loss of connectivity among its areas) (Tijms et al., 2013).

Anosognosia, a common problem observed in AD patients, has also been related to the activation of CMSs. Ries et al. (2012), for example, found that the recruitment of these regions in MCI subjects was diminished during self-appraisal activities, and this activation correlated with the cognitive self-awareness deficit in the subjects. Another recent study that combined measures of regional brain metabolism and intrinsic connectivity (Perrotin et al., 2015) related anosognosia in AD patients not only to functional changes within the CMSs but also to disconnection between these regions as well as with the medial temporal lobe.

The DMN can also be identified by high temporal resolution time series methodology (EEG and MEG), in which a spatial pattern of spectral band power modulation consistent with the fMRI pattern can be observed (Fomina et al., 2015). Some studies have shown that patients with AD, similarly to results obtained by fMRI studies, present weaker functional connectivity in regions of the DMN. For instance, Hsiao et al. (2013) reported electrophysiological alterations of cortical spectral power in DMN areas as well as altered functional interconnections in the precuneus, posterior cingulate cortex, anterior cingulate cortex, and medial temporal regions in mild AD patients. Similarly, MEG studies have found functional disruption in temporal areas (de Haan et al., 2012) and key regions of the DMN (Canuet et al., 2015).

5. The resting state

CMSs, which are the core regions of the DMN, show particularly interesting neuronal activity when any individual is left alone and undisturbed. These moments were initially called the 'resting state' or 'baseline activity' because it was said that the brain was resting and thus not engaged at any cognitive task. Also, neuroimaging studies have shown that the MPFC is among the regions having the highest baseline metabolic activities at rest (Raichle et al., 2001), and when external attention is required or the subject engages in cognitive tasks the DMN activity is attenuated (thus called 'task-negative network') (Gusnard and Raichle, 2001). During baseline activity, the brain is in a highly organized spontaneous pattern that consumes most of the brain's energy (Raichle and Mintun, 2006), contrasting to task-related activation, which accounts for <5% of the total blood oxygen-level-dependent (BOLD) signal and requires only a small percentage of neurons (Biswal et al., 1995). For this reason, it has been said that the rest activity states contain complex, structured brain activity patterns that may support important brain functions. If so, what is the purpose of such intrinsic and organized activity? Although it is tempting to assume that it reflects simply housekeeping functions such as neuronal repair, its functions may go beyond them.

During these 'passive states', the subjects engage in spontaneous cognition and experience mainly monitoring of the external environment and body state (Gusnard and Raichle, 2001), stimulus-independent thought (Buckner et al., 2008), problem-solving (Binder et al., 1999), retrieval and consolidation of past experiences, and planning and preparing for the future (Andreasen et al., 1995; Buckner and Vincent, 2007). It is also interesting to note the human propensity for engaging in these inner thoughts and easily shifting attention away from primary tasks. Such easily achievable mental states are characterized by a substantial amount of self-referential thought, making us think that when left undisturbed, one is processing self-related information. Indeed, studies have shown that the CMSs mediate internally-oriented self-relatedness (Schneider et al., 2008), and these regions overlap with the resting state (Qin and Northoff, 2011). Furthermore, the network is composed by different and interacting subsystems that correlate with the CMSs: a medial temporal subsystem (related to ABMs, episodic memory, and contextual retrieval) and a dorsal medial subsystem (related to social cognition, story comprehension, and conceptual processing) (Andrews-Hanna et al., 2014).

But what is the nature of the processing of self-related information during rest? Very interesting studies showing the interaction between resting periods and stimuli can shed some light in the present discussion. For instance, adults that were submitted to intense visual training had increased functional connectivity at rest between networks engaged by the task that correlated with the degree of perceptual learning (Lewis et al., 2009). Another study investigated the effects of motor learning on resting state activity and reported that the functional connectivity in the motor system increased after the subjects learned a novel task (Albert et al., 2009). Two other studies involving rats trained to run in a maze provided clues about how resting state activity may relate to learning episodes. While the rats were resting after the task, the cells recruited by the task spontaneously fired with the same sequential patterns as when actually performing the task, but they fired much faster and in the reverse order (Foster and Wilson, 2006; Diba and Buzsaki, 2007). Although the resting state activity may be responsible for maintaining the system's alertness and preparing to provide rapid responses when required, the intrinsic neuronal activity and learning-related functional connectivity changes during rest suggest that some form of consolidation may take place during these periods, such as memory consolidation (Vincent, 2009). If the connectivity of the above-mentioned cognitive networks supports the consolidation of previous experience that engaged the network, why not assume the same for other resting-state circuits such as the DMN?

Similarly to the theories that have been raised to explain the DMN function, the resting-state activity has also been related to monitoring the external world. However, the strong association between the rest and self-referential processing makes us think about an off-line consolidation of memories (Miall and Robertson, 2006), leading to a more introspective function of rest. The MPFC, for instance, exhibits a higher activity when a subject has to refer to internal states compared to external states, and the activity is even greater when the subject is at rest (Wicker et al., 2003). Thinking about one's personality traits (D'Argembeau et al., 2005) and the retrieval of episodic ABMs (Andreasen et al., 1995) were associated with common activation in the vMPFC during resting states in positron emission tomography studies. Also, the overlap between the self and resting state found in a meta-analysis study suggests that self-specificity seems to be encoded in the resting states' neural activity (Northoff, 2012), *i.e.*, the Default Mode Network processing. For such reasons, the resting state has been considered the ultimate state of inspection of the self, enabling one to represent knowledge pertaining to oneself and helping them to maintain a stable self-concept overtime (D'Argembeau et al., 2005).

The formation and updating of the self, similarly to a novel task learned, consists of the linkage and interaction between the mind's intrinsic features and the environment's external stimuli. It cannot be reduced to the internal origin only, neither can it be defined with purely external origin (Qin and Northoff, 2011). The resting state is somehow needed to integrate the external stimuli with the inner information, and this interaction is necessary to generate the stimulus-specific activities (Northoff et al., 2010). It is known that the DMN is activated during rest; these periods are characterized by high self-related processing. It might be that during rest the DMN consolidates self-related information through mental activities like time travelling, planning, personal problem solving, self judgments, and so on. It might be that our personal experiences – the external stimuli – are linked together and processed during resting periods (Qin and Northoff, 2011) by the DMN, and without them we would not be able to properly piece together our ABMs or compose and understand our life history. It might be that resting periods are necessary for processing personal events, and a healthy DMN is needed for the formation and updating of the self concept.

Diseases such as schizophrenia and depression, for example, affect the individual concept of self, which has been related to alterations in spatiotemporal continuity. While schizophrenic patients can be characterized by spatiotemporal disruption and fragmentation, depressed patients present spatiotemporal dysbalance (Northoff, 2014a). As the above discussion exemplified, AD patients also present several alterations in many aspects of the self, tending to freeze it in time and originating a 'petrified' self (Mograbi et al., 2009). Although it is tempting to say that AD patients are not able to update their self-knowledge probably because of their widely known episodic memory deficit, it might be that an inefficient resting state functioning causes those alterations, as it has been postulated for schizophrenia and depression (Northoff, 2014a).

Earlier, we presented many findings regarding CMSs and more specifically DMN alterations in functional connectivity, metabolism, and amplitude of low frequency fluctuations in AD patients. It has been postulated that the linkage between discrete points in physical time (and thus making one experience a temporal continuum between the different contents, *i.e.*, the 'form' of

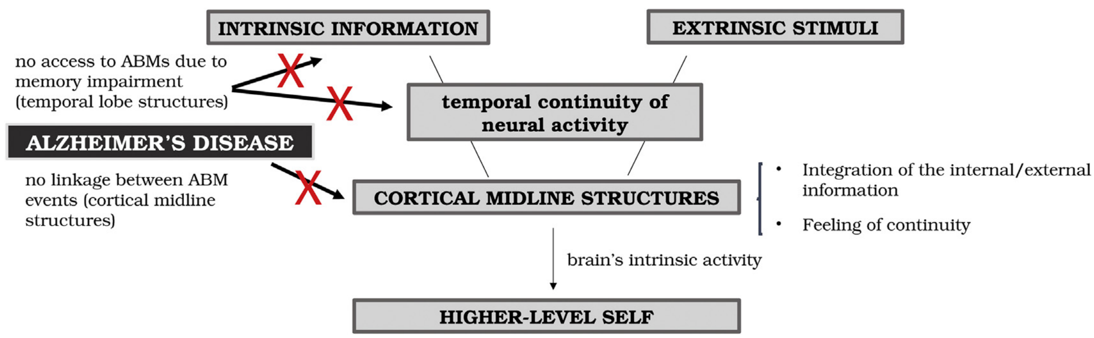

Fig. 1. The updating of the old/internal by the new/external information is processed by the cortical midline structures (CMSs) during resting periods (brain's intrinsic activity). Resting periods are necessary for personal events processing, and a healthy CMSs unit (*i.e.*, Default Mode Network processing–DMN) is needed for the formation and updating of the self. AD patients besides having no longer access to the autobiographical memories (ABMs) due to memory impairment, present alterations in the CMSs/DMN low frequency fluctuations and functional connectivity (*i.e.*, the brain's intrinsic activity). Thus, they no longer link the different events of the ABM events and no longer experience a temporal continuum, shifting towards the past and presenting self-awareness alterations.

consciousness) is made by low frequency fluctuations and functional connectivity (Northoff, 2013, 2014b). Abnormalities in the resting state's intrinsic organization can lead to alterations in the way the brain processes these different and discrete points in physical time, making one no longer experience temporal continuity in their consciousness (Northoff, 2014a). For AD patients, specifically, it would be as if their brains are always in a 'disorganized' resting state, lacking a proper conversation between the DMN areas and consequently the self-focused spontaneous thought typical during resting state periods. If the role of the DMN during rest is to properly make self-referential processing, miscommunications between the DMN regions might cause the self-related problems faced by AD patients, because there is no longer updating of the old/internal by the new/external information. The role of hippocampal and other medial temporal lobe structures in episodic memory is undeniable, but the integration of that information into a coherent picture, which is necessary for the updating of the self-referential database, seems more like a network function. The new/external stimuli may encounter an already altered temporospatial continuity when interacting with the brain's intrinsic activity (Northoff, 2014a, 2015). Thus, AD patients lose the ability to update their self-knowledge, failing to integrate the self into a coherent and meaningful picture.

It might be important to mention how complex it is to define and to attribute brain areas to the self. In the present text, we do not intend to reduce the feeling of temporal continuity and the sense of self-awareness as a function uniquely of the CMSs. Philippi et al. (2015) for example, have reported that although damage to the regions of the DMN was associated with ABM impairment, damage in some DMN areas was not enough to cause self-unawareness and to disrupt the higher-order metacognitive abilities in a rare neurological patient (Philippi et al., 2012). Instead, other important networks may interact with the DMN when maintaining internal thoughts such as the executive control (for more details see (Andrews-Hanna et al., 2014)), in which the systems interact in a much more complex way.

6. Conclusions

The human sense of self comprises multiple facets or levels, ranging from the consciousness of oneself as an immediate subject of experience to the construction of oneself as a distinct entity with a personal history. AD patients present alterations in many aspects of the self, which include the higher-level self-awareness. Since self-awareness seems to be closely related to self-continuity, and self-continuity is inseparable from memory, it is tempting to say that only memory problems could be responsible for the alterations in the feeling of being continuous in time. However, we here assume that self-related alterations presented by AD patients go beyond episodic memory recall made by the hippocampus and include [b1] network functions. The feeling of being continuous in time stems from DMN/CMSs processing during resting state periods, and, without the correct processing and communication between its regions, there is no proper ABM recall, feeling of self-continuity, or narrative self. It is the resting state activity (especially the DMN/CMSs processing) that constructs the continuity of time that underlies any subsequent cognitive function, including ABM retrieval. Thus, by constructing and feeling temporal continuity (*i.e.*, stream of consciousness), one can experience self-continuity and ABM recall. The construction of the continuity of time is essential for ABM retrieval, which, in turn, is a precondition for updating the self. (Fig. 1).

Conflict of interest

The authors report no conflict of interest.

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