Disrupted Self in Alzheimer's disease: beyond midline structures

Commentary on Wong et al.

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Midline structures of the brain are thought to be essential to self-related processes. In particular, medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC) play a crucial role in the self concept. This hypothesis mainly comes from the wealth of PET and fMRI studies showing activations in ventral MPFC/ACC during judgment with self-reference in healthy people (D'Argembeau et al., 2005; Northoff et al., 2006). Subsequent studies have further suggested that the ventral MPFC/ACC should be activated when "crystallized" aspects of the self (i.e. self concept/conceptual self) are engaged (Martinelli et al., 2012). In patients with Alzheimer's disease (AD), one can assume that altered self reference effect (SRE), i.e. the absence of memory advantage for information that has been previously linked to the self at encoding, can be related to functional or structural perturbations of a conceptual self or "core self". However, this hypothesis has been challenged by a study showing that AD did activate MPFC during a traditional self reference task (Genon, Bahri, et al., 2014; Genon, Bastin, et al., 2014) and a recent replication by Gaubert et al. (2016). Accordingly, when Wong et al. (in press) searched for correlation between individual SRE and grey matter volume (GMV) variability specifically within midline structures, they did not find a significant ***specific*** role of the ventral MPFC/ACC in a mixed group of AD and healthy controls. Thus, many studies converge to show that altered SRE in AD is not directly related to **local** functional and/or structural damage to ventral MPFC/ACC.

Several authors hypothesized that damage to the posterior midlines structures, i.e. Posterior Cingulate Cortex (PCC) and precuneus play a role in altered self-related processes in AD (Perrotin et al., 2015; Weiler et al., 2016). Given the complex PCC "hub" role in functional systems (Leech & Sharp, 2014), damages to the PCC/precuneus in AD could disrupt the dynamic functional interaction between two neurocognitive systems: self and memory. In a seminal study, such an hypothesis was not confirmed during retrieval of self-related compared to other-related items in AD (Genon, Bahri, et al., 2014), nor was it evidenced with a further multivariate approach (Genon, Bastin, et al., 2014). Other authors have similarly failed to find evidence for the functional role of the PCC/precuneus during the retrieval of self-related items when compared to the retrieval of other-related items in early AD (Gaubert et al., 2016). Thus, the functional neuroimaging tools and

analyses in these reports did not allow to provide evidence for a role of the PCC/precuneus in the disrupted interaction between self and memory neurocognitive systems in AD. Wong et al. found a significant relationship between reduced SRE and reduced GMV in posterior middle cingulate cortex (MCC; MNI coordinates: 16 -36 38, which is close to Area 5Ci according to SPM Anatomy toolbox and matches to MCC in the Harvard-Oxford atlas) in the mixed group of healthy participants and AD. However, this finding did not allow understanding the involvement of the posterior part of the cingulate cortex (PCC sensu stricto) in the impaired interaction between self and memory leaving the question of the role of the PCC in impaired SRE in AD open. However, one could assume reduced SRE to be related to altered large-scale functional connectivity (FC) of the PCC (and/or ACC) in AD. Partially supporting this view, Perrotin et al. (2015) have shown that altered FC of the midline structures could be related to impaired memory awareness (and maybe therefore to impaired interaction between self and memory systems) in AD. To further investigate this issue, on the one hand, recent developments in capturing dynamic FC over resting-state period in fMRI (e.g. (Liegeois et al., 2016)), and on the other hand, recent evidence that individual behavioral measures can be related to the FC fingerprint (Finn & Constable, 2016; Finn et al., 2015) open new perspectives for understanding whether and how impaired SRE relates to altered FC in AD.

Several cognitive mechanisms related to disrupted interaction between self and memory have been identified in recent years. Actually, linkage to the self influences several aspects of cognition beyond memory, such as perception and decision making (Sui & Humphreys, 2015). Relatedly, disrupted interaction between self and memory in AD is related not only to lower recognition performance for self-related memories in AD, but also to impoverished recollective experience (Genon, Bahri, et al., 2014) and poor source memory (Wong et al., in press). Our previous study has revealed that reduced individual SRE could be related to lower GMV in lateral prefrontal cortex in AD allowing the hypothesis of altered monitoring processes of self-associated information in these patients (Genon, Bahri, et al., 2014). Gaubert et al. (2016) found a relationship between lateral parietal activation at encoding and SRE (at retrieval) in early AD participants, hence further suggesting that the complex interplay between self and memory-related system may engage several neurocognitive mechanisms beyond midline cortical structures robustly engaged in self and memory. Wong et al. (2016) did not search for neural correlates of altered cognitive processing of self-related memories beyond midline structures leaving this issue unconfirmed. Thus, future studies should address the range of cognitive privileges of the self that are undermined by AD pathology, as well as their neural correlates within ***and beyond*** midline structures.

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