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Behavioural-variant frontotemporal dementia: a unique window into the disrupted self

Reply to Genon & Salmon

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We read with interest the commentary by Genon & Salmon (2017) on our study of the self-reference effect on memory in Alzheimer's disease and behavioural-variant frontotemporal dementia (bvFTD) (Wong et al., 2017). Our findings indicate that, although the benefit of self-referential processing on memory retrieval is comparably reduced across both patient groups, these deficits reflect divergent patterns of atrophy in cortical midline structures (CMS).

We agree with Genon & Salmon that, while it is widely accepted that CMS regions are involved in self-referential processing, it is also clear that we must consider regions beyond the CMS. For example, Northoff & Bermpohl (2006) suggest that the lateral prefrontal cortex may be necessary for interactions between self-referential and higher-order cognitive processes. More recent work has highlighted the importance of three key neural networks in the integration of perceptual, cognitive and affective aspects of self-referential processing, including the core 'self network' (medial prefrontal cortex), 'cognitive control network' (lateral prefrontal cortex and superior temporal sulcus) and 'salience network' (insular, amygdala and striatum) (Sui & Gu, 2017). It would be remiss, however, to discount the contribution of posterior CMS regions—such as the posterior cingulate cortex (PCC)—to self-referential processing in Alzheimer's disease, given its well-documented involvement in self-generated thought (Andrews-Hanna, Smallwood, & Spreng, 2014; Herbet et al., 2014) and the retrieval of self-related memories (Irish, Addis, Hodges, & Piguet, 2012; Philippi, Tranel, Duff, & Rudrauf, 2015; Summerfield, Hassabis, & Maguire, 2009).

Studying patients with Alzheimer's disease has, to an extent, advanced our understanding of the interactions between the self and memory. To truly capture the complexity of self-related memories, however, it is necessary to consider patient groups where the pathological process

directly targets those structures known to be critical for self-referential processing. In particular, converging evidence from functional neuroimaging and lesion studies (Gutchess, Kensinger, Yoon, & Schacter, 2007; Leshikar & Duarte, 2012; Philippi, Duff, Denburg, Tranel, & Rudrauf, 2012) emphasise the importance of anterior-ventral CMS regions—such as the medial prefrontal cortex (mPFC)—for the initial coding of stimuli as self-relevant (Northoff et al., 2006; Northoff & Bermpohl, 2004). According to the model proposed by Northoff and colleagues (2006; 2004), the mPFC functions as a critical hub for the formation of self-related representations, which may then be evaluated and/or integrated through downstream processes mediated by anterior-dorsal and posterior CMS regions, respectively. In this context, the syndrome of bvFTD offers a unique opportunity to investigate self-referential processing, as striking mPFC atrophy is evident from the earliest stages of the disease (Kipps, Hodges, Fryer, & Nestor, 2009; Rabinovici et al., 2007; Seeley et al., 2008).

Importantly, bvFTD represents a prototypical disorder of the self. Patients present with marked changes in personality and temperament (Piguet, Hornberger, Mioshi, & Hodges, 2011), often showing striking discrepancies in self-concept and awareness (Rankin, 2005; Ruby et al., 2007) and personal values (Miller et al., 2001). Reductions in self-conscious emotional responses, which rely upon the capacity to monitor the self in relation to others, have also been reported (Sturm, Ascher, Miller, & Levenson, 2008). These changes are typically accompanied by a lack of insight (Mendez & Shapira, 2011; O'Keefe et al., 2007) and declines in social cognitive processes such as empathy and prosocial reasoning (Dermody et al., 2016; Eslinger, Moore, Anderson, & Grossman, 2011; Sturm et al., 2017). Furthermore, these self-related and social cognitive changes have well-established neural correlates in the anterior-ventral CMS hub of the Northoff et al., model (2006; 2004).

In contrast, such striking personality and social cognition changes are rarely observed in Alzheimer's disease, particularly in the early disease stages, with individuals continuing to display their premorbid personality, sense of identity and preferences (Eustache et al., 2013; Halpern, Ly, Elkin-Frankston, & O'Connor, 2008; Klein, Cosmides, & Costabile, 2003; Rankin, 2005; Tappen, Williams, Fishman, & Touhy, 1999). While some patients may show deficits in current self-knowledge, these changes are more likely to reflect an older version of the self from the epoch in which the individual is remembering and not a change in their personality and behaviour per se (Eustache et al., 2013; Morris & Mograbi, 2013). This preservation of premorbid personality is largely held to reflect the relative sparing of the medial prefrontal regions during the early to moderate stages of the disease (Frisch et al., 2013; Irish, Piguet, Hodges, & Hornberger, 2014). Although atrophy of these regions emerges with disease progression (Landin-Romero et al., 2017), longitudinal studies are required to establish the impact of these changes on self-referential processing.

Hence, our recent approach has been to contrast different disease groups to allow us to examine the nature of altered self-referential processing in dementia, and the corresponding neural substrates which drive these changes. We propose that in order for the field to move forward, cross-comparative studies of different disease groups with divergent underlying neural damage are critical and complement single patient group studies, which investigate phenotype specific changes in more depth. In this context, our study is the first to demonstrate that anterior versus posterior neural damage differentially impacts self-referential processing in bvFTD and Alzheimer's disease. Future studies that contrast the functional activity and connectivity between and beyond these CMS regions will serve to further clarify the wider neural network changes across these patient groups. Characterising

such changes across dementia syndromes will pave the way to truly understanding the cognitive and neuroanatomical underpinnings of the disrupted self.

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