A Partial Least Squares Analysis of the self reference effect in Alzheimer's disease: A reply to Irish

Sarah Genon[1,2,3], Christine Bastin[1], Lucie Angel[5], Fabienne Collette[1], Mohamed Ali Bahri[1*] and Eric Salmon[1,4*]

* Equally contributed

[1] Cyclotron Research Centre, University of Liège, Belgium

[2] Institute of Neuroscience und Medicine (INM-1), Research Centre Juelich, Juelich, Germany

[3] Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine University, Düsseldorf, Germany

[4] Memory Centre, CHU Liège, Belgium

[5] University François-Rabelais of Tours, UMR CNRS 7295 CeRCA, Tours, France

Introduction

Recent evidence suggests that the interaction between self and memory may be impaired in some AD patients as reflected by impaired self reference effect (SRE), self reference recollection effect (SRRE) and impaired retrieval of contextual details for self-related information in AD patients (Genon et al., in press). In a recent study, we suggested that self-referential processing at encoding is related to the engagement of the ventromedial prefrontal cortex (VMPFC) in AD patients as it is in healthy older people, whereas reduced and variable SRE in AD patients is related to grey matter volume reduction in the lateral prefrontal cortex (LPFC) across the middle and superior frontal gyri (Genon et al., in press).

In a relevant commentary on our study, Irish (in press) insightfully raised the issue of the medial temporal lobe and posterior cingulate cortex (PCC)'s role in the impaired interaction between self and memory in AD patients. Indeed, given the severe impairment of episodic memory and the brain perturbations in the related brain network including the medial temporal lobe and the posterior cingulate cortex in those patients (Buckner et al., 2005), one might have expected a relationship between the pathology in these regions and impaired memory retrieval for self-referential information in AD patients. Hence, in our study,

univariate analyses of brain activity during self-referential encoding and retrieval of self-related information did not highlight brain activations in this posterior network neither in healthy older people nor in AD patients. Moreover, a correlation analysis between SRE scores and grey matter density failed to evidence a predominant role for these regions in self-related memory performance of AD patients but rather put forward the role of lateral prefrontal regions.

In healthy people, recollective processes during memory retrieval are associated with the engagement of several brain regions (including the VMPFC, the hippocampus and the PCC) acting in concert and thus forming a complex brain network (Rugg and Vilberg, 2013). Importantly, Alzheimer pathology is characterized by modifications of white matter tracks related to disruption between core regions within this complex cerebral network (Villain et al., 2010). Therefore, the exploration of task-related functional activity in AD patients should take into account impairment in brain interregional interactions (this issue is even more crucial when examining complex cognitive phenomena such as the interaction between self and memory). In this context, Partial Least Squares (PLS) has been developed to allow identifying functional networks differentially engaged across different task conditions (McIntosh et al., 1996). This multivariate technique has then been applied to various task-related functional data (Spreng et al., 2010; Spreng and Grady, 2010; Burianova et al., 2012; Addis et al., 2012). In the present study, we used PLS to address similar issues to those examined in our previous study (Genon et al. in press) but with a focus on functional networks rather than on regional involvement. By using task PLS, we searched for 1) spatial pattern of self-referential vs other-referential processing at encoding and 2) spatial and temporal pattern of successful retrieval of self-related vs other-related items. Furthermore, we also introduced SRE scores as a behavioral measure of interest by performing behavior PLS to identify functional networks whose activity co-varies with SRE performance at encoding during self-referential judgments and during retrieval of self-related items.

Methods

For a description of participants, materials, experimental task, images acquisition and preprocessing, see Genon et al. (in press).

PLS analyses

Data were analysed with partial least squares (PLS), a validated (McIntoch et al., 1996; McIntoch and Lobaugh, 2004) multivariate approach that robustly identifies whole brain activity patterns correlated with experimental design (i.e., conditions or tasks). PLS has been widely used in studies on autobiographical memory and related processes (Burianova and Grady, 2007; Burianova et al., 2010; Spreng et al., 2010; Addis et al., 2012). It can be used either for extracting distributed signal changes related to varying task demands (Task PLS) or for measuring distributed patterns that impact on task performance (Behavior PLS; McIntosh & Lobaugh, 2004). PLS assesses the covariance between brain voxels and the experimental design to identify a set of orthogonal components called Latent Variables (LVs). Each of these LVs identifies pattern of differences in brain activity across the tasks and the brain voxels showing this effect. The significance of each LV is determined using a permutation test (Edgington, 1980; McIntosh et al., 1996). Each brain voxel has a weight (so-called salience) on each LV that indicates the extent to which that voxel is related to the LV. Depending on whether the voxel shows a positive or negative relation with the pattern identified by the LV, the salience can have a positive or negative value. The reliability of the saliences for the brain voxels characterizing each LV is determined using the bootstrap estimation of the standard errors (Efron and Tibshirani, 1986; Sampson et al., 1989). The salience/standard error ratio (BSR) was calculated for each voxel. PLS calculate all saliences in a single analytic step, so there is no need to correct for multiple comparisons as in univariate analyses (McIntosh et al., 1996).

In this study, we applied PLS to blocked (encoding) and event-related (recognition) fMRI data. The first analysis included blocked fMRI data (encoding) for self- and other-referential conditions, and consisted in examination of spatial pattern of differences in brain activity across the two conditions using Mean-Centring PLS. We next carried out a behavior PLS analysis on the same data and using the SRE performance at encoding during self-referential judgments as behavioral data (behavior PLS).

The second analysis was performed on the event-related fMRI data (recognition) for successful retrieval of self- and other-related items (self_hits and other_hits). Mean-Centering PLS was used to investigate brain regions wherein activity is reliably related to these events at 8 post-stimulus time points (8 TRs = 16 s) for each LV. Given that the maximum response time to recognition items was 5 sec. in our experiment, only lags corresponding to the peak of the standard hemodynamic response function, approximately 4 to 6 s after stimulus onset

(Aguirre et al., 1998) have been considered (that is, lag 1 to lag 3). A behavior PLS analysis was also carried out on these recognition data using the SRE performance as behavioral score. For all analysis, the significance of LV was determined using 600 permutations and the reliability of the saliences for brain voxels characterizing each pattern identified by a LV was determined with bootstrap sampling technique using 100 iterations. Clusters containing at least 10 voxels with a BSR equal to or greater than 3.3 ($p < .001$) were reported.

Results

Task PLS

Encoding

One significant LV ($P<.05$) accounting for 68% of the cross-block covariance was identified in the Mean-Centering PLS analysis. This significant LV identified a functional brain network including ventromedial, dorsomedial, ventrolateral and dorsolateral prefrontal cortices, but also orbitofrontal, superior parietal and lateral temporal cortices that showed greater activity during self-referential encoding blocks in HC participants and AD patients. These brain regions in which activity positively co-varies with this pattern in both groups are reported in Table 1 and illustrated in Figure 1.

[Table 1 and Figure 1 about here]

Retrieval

The Mean-Centering PLS analysis revealed one significant LV ($P<.01$) accounting for 77% of the covariance. This LV identified brain regions differentiating self_hits and other_hits in AD patients. Most of the significant brain activations were identified at lag 2 (4 seconds after item presentation). These brain activations are located within the left hippocampus, the left inferior frontal gyrus, the left occipital cortex, the right anterior parietal cortex and the PCC (see Table 2 and Figure 2).

[Table 2 and Figure 2 about here]

Behavior PLS (SRE scores as behavioral measure of interest)

Encoding

A regular behavior PLS analysis on encoding blocks yielded no significant LV.

Retrieval

A regular behavior PLS analysis yielded no significant LV.

Discussion

The multivariate analysis of brain activations related to self referential processing of traits adjectives in HC participants and AD patients at encoding revealed a wide brain network involving mainly the prefrontal cortex. Notably, this network included the peak of activation in the left VMPFC (MNI coordinates: -12 42 4) found in both HC and AD during self-referential processing in a previous univariate analysis of the data (Genon et al., in press). According to current theories, within the prefrontal cortex, the VMPFC is the only self-specific region, supporting self-referential judgments per se, that is, coding the self-relatedness of stimuli (Northoff et al., 2006; Wagner et al., 2012). In contrast, the engagement of the dorsal parts of the medial prefrontal cortex (DMPFC) during self-referential traits judgments might reflect the involvement of appraisal/inferential evaluation processes (D'Argembeau et al., 2007; Northoff et al., 2006).

The functional brain network associated with judgment of adjectives in reference to the self also included lateral prefrontal regions. Brain activations in these regions might reflect the recruitment of numerous and various high-order/monitoring processes (Northoff et al., 2006). However, there was no overlap with the cluster (MNI coordinates: 30 45 4) previously identified by the correlational analysis between variations of SRE performance and grey matter density in AD patients (Genon et al., in press). In addition, the functional brain network related to self-appraisal included activation of orbitofrontal regions which might be related to the engagement of emotional and decision making processes (Volz and von Cramon, 2009), activation of the lateral temporal cortex which might support retrieval of semantic representations (Rogers et al., 2006) and activation of the superior parietal cortex

which may reflect the involvement of either attentional (Cabeza et al., 2011) or memory retrieval processes (Kim, 2010).

The mean-centering PLS analysis of recognition data identified some brain regions that showed differential activity for successful retrieval of items encoded in reference to the self (self_hits) and successful retrieval of items encoded in reference to other (other_hits) in AD patients. Namely, the inferior frontal gyrus, the superior parietal cortex, the PCC and the hippocampus showed brain activations positively related to successful retrieval of self-related items in AD patients. Whereas activation of the inferior frontal gyrus and superior parietal cortex may reflect the use of task positive attentional processes (Fox et al., 2005), the recruitment of the PCC and the hippocampus might be related to an episodic memory retrieval mode (Rugg and Vilberg, 2013). Thus, as suggested by Irish (in press), the PCC and the hippocampus may play a role in memory retrieval of self-related information. However, by using behavior PLS, we did not find that activations in these regions co-varied with memory advantage for self-related information (i.e. SRE performance). In other words, although AD patients activated the hippocampus and the PCC when retrieving information encoded in reference to the self, our results did not put forward a crucial role for these regions in SRE.

Altogether, the previous findings highlighting a relationship between the memory advantage for self-related information and the LPFC (Genon et al., in press), and the present finding suggesting that the PCC does not play a crucial role in impaired SRE in AD patients, invite us to carefully reconsider how self and episodic memory interact. Several studies have found PCC activation during self-referential processing (Northoff et al., 2006). This has usually been interpreted in terms of episodic memory retrieval during judgments about oneself (Northoff et al., 2006). The PCC might be an important node which supports episodic memory retrieval, thus providing materials that feed self-referential judgment. However, this does not mean that the PCC plays a crucial role in the reverse issue, that is, the influence of self on episodic memory. In other words, the PCC may not play an important role in the influence of self-referential processing on subsequent memory retrieval. Our previous findings in AD patients suggest that the SRE may be preserved in some of these patients (Genon et al., in press). In the same vein, the case of an amnesic patient (presenting both episodic and semantic memory impairments) with preserved SRE has been recently reported (Sui & Humphreys, 2013). These observations suggest that the SRE cannot be reduced to a matter of memory, but that the SRE is a phenomenon that includes some self-specific aspects,

probably related to prefrontal regions as suggested by our previous findings (Genon et al., 2013).

One potential limitation of the study of interaction between self and memory in AD is the high inter-individual variability of the SRE in these patients. In a previous study (Genon et al., in press), this variability allowed performing correlational analyses, which revealed a positive relationship between SRE and grey matter density in the lateral prefrontal cortex. Even so, when examining functional activity, this variability may prevent finding a uniform pattern of brain perturbations related to impaired SRE in some AD patients. This issue might be addressed with larger samples of AD patients and clustering of these patients according to the preservation or the disruption of the SRE. Such procedure should allow comparing brain functioning of AD patients showing a SRE in memory and brain functioning of those showing no self reference effect. Future studies are thus needed for characterizing the functional brain network related to impaired interaction between self and memory at the retrieval stage in AD patients.

Funding

The authors report no conflict of interest. This work was supported by the Belgian National Fund for Scientific Research (FRS-FNRS) and the Fonds Leon Fredericq.

References

Addis DR, Knapp K, Roberts RP, and Schacter DL. Routes to the past: Neural substrates of direct and generative autobiographical memory retrieval. *NeuroImage*, 59: 2908-2922, 2012.

Aguirre GK, Zarahn E, and D'Esposito M. The variability of human BOLD hemodynamic responses. *NeuroImage*, 8: 360–369, 1998.

Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, et al. Molecular, structural, and functional characterization of Alzheimer's disease: Evidence for a relationship between default activity, amyloid, and memory. *The Journal of Neuroscience*, 25(34): 7709-7717, 2005.

Burianova H. and Grady CL. Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *Journal of Cognitive Neuroscience*, 19: 1520–1534, 2007.

Cabeza R, Mazuz YS, Stokes J, Kragel JE, Woldorff MG, Ciaramelli E, et al. Overlapping parietal activity in memory and perception: evidence for the attention to memory model. *Journal of cognitive neuroscience*, 23(11): 3209-3217, 2011.

D'Argembeau A, Ruby P, Collette F, Degueldre C, Balteau E, Luxen A, et al. Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective taking. *Journal of Cognitive Neuroscience*, 19(6): 935-944, 2007.

Edgington ES. Randomization tests. New York: Marcel Dekker, 1980.

Efron B and Tibshirani R. Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. *Statistical Science*, 1: 54–77, 1986.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, and Raichle ME. The human brain is instrincisally organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, 102(27): 9673-9678, 2005.

Genon S, Bahri MA, Collette F, Angel L, d'Argembeau A, Clarys D, et al. Cognitive and neuroimaging evidence of impaired interaction between self and memory in Alzheimer's disease. *Cortex*, in press.

Irish M. Mental reliving and the self: Commentary on Genon et al. *Cortex*, in press.

Kim H. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *Neuroimage*, 50(4): 1648-57, 2010.

McIntosh AR, Bookstein FL, Haxby JV, and Grady CL. Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage* 3(3): 143-57, 1996.

McIntosh AR and Lobaugh NJ. Partial least squares analysis of neuroimaging data: applications and advances. *NeuroImage*, 23, 250–263, 2004.

Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, and Panksepp J. Self-referential processing in our brain- a meta-analysis of imaging studies on the self. *Neuroimage*, 31(1): 440-57, 2006.

Rogers TT, Hocking J, Noppeney U, Mechelli A, Gorno-Tempini ML, Patterson K, et al. Anterior temporal cortex and semantic memory: reconciling findings from neuropsychology and functional imaging. *Cognitive, Affective, & Behavioral Neuroscience*, 6(3): 201-213, 2006.

Rugg MD and Vilberg KL. Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology*, 23(2): 255-60, 2013.

Sampson PD, Streissguth AP, Barr HM, and Bookstein FL. Neurobehavioral effects of prenatal alcohol: Part II. Partial least squares analysis. *Neurotoxicology and Teratology*, 11(5): 477–491, 1989.

Spreng RN and Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory-of-mind and their relationship to the default mode network. *Journal of Cognitive Neuroscience, 22*: 1112–1123, 2010.

Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, and Schacter DL. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *NeuroImage,* 53, 303–317, 2010.

Sui J and Humphreys GW. Self-referential processing is distinct from semantic elaboration : evidence from long-term memory effects in a patient with amnesia and semantic impairments. *Neuropsychologia*, 51, 2663-2673, 2013.

Villain N, Fouquet M, Baron JC, Mézenge F, Landeau B, de La Sayette V, et al. Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain,* 133(11): 3301-3314, 2010.

Volz KG and von Cramon DY. How the orbitofrontal cortex contributes to decision making - a view from neuroscience. *Progress in Brain Research*, 174: 61-71, 2009.

Wagner DD, Haxby JV, and Heatherton TF. The Representation of Self and Person Knowledge in the Medial Prefrontal Cortex. *Wiley Interdisciplinary Reviews: Cognitive Science*, 3(4): 451-470, 2012.

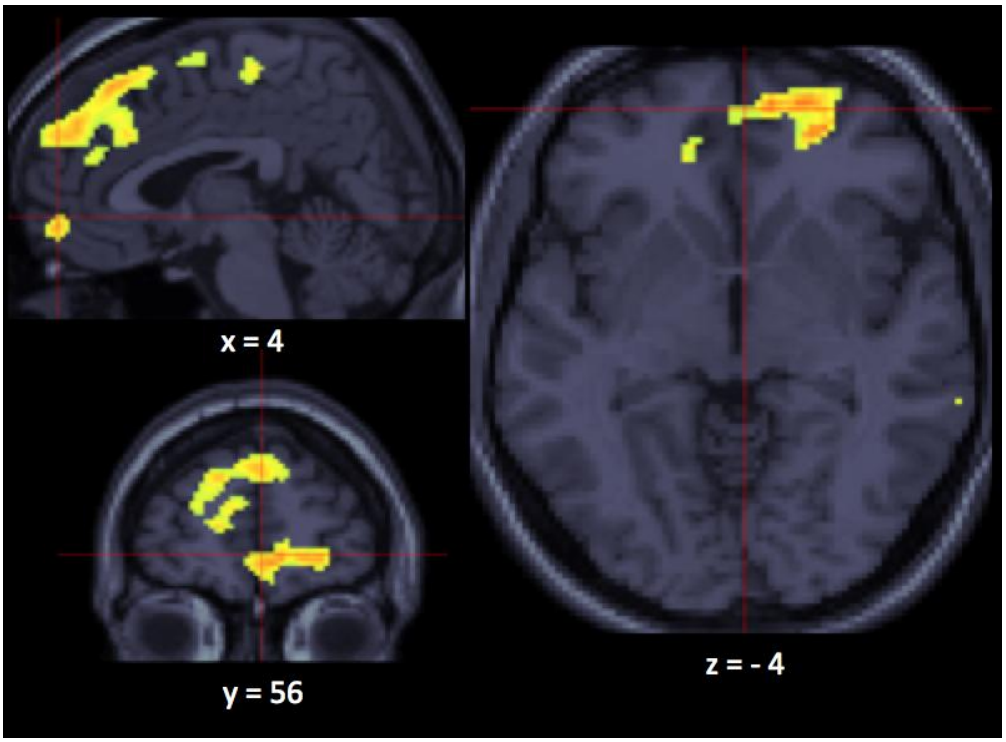

Figure 1. Brain regions (from LV1) related to the main effect of self-referential encoding vs. other-referential encoding in HC participants and AD patients.

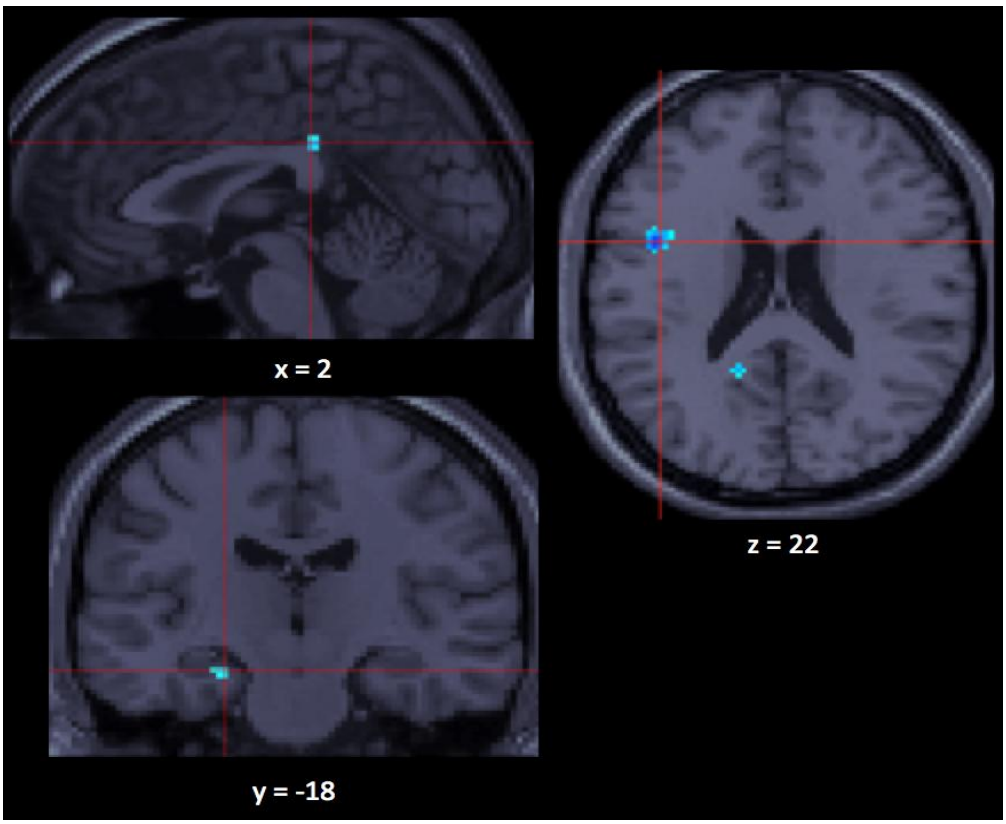

Figure 2. Brain regions (from LV1) positively associated to the successful retrieval of self-related items (self_hits vs other_hits) at lag 2 in AD patients.

Table 1.

Brain network (from LV1) related to the main effect of self-referential encoding vs other-referential encoding in HC and AD patients.

Region	Side	MNI coordinates			Cluster size	BSR
		x	y	z		
Ventromedial prefrontal cortex	L	-14	40	0	139	5.37
Dorsomedial prefrontal cortex	R	14	-14	58	6438	6.09
Ventrolateral prefrontal cortex	R	26	50	-6	607	5.13
		24	62	10	169	4.49
	L	-32	52	0	25	3.80
Dorsolateral prefrontal cortex	L	-22	24	52	4168	6.08
		-46	22	12	36	4.53
		-56	30	18	61	4.19
	R	40	18	26	34	3.84
	R	42	28	32	36	3.90
Orbitofrontal cortex	R	40	40	-20	59	4.09
		26	12	-16	10	3.70
	L	-32	34	-16	45	3.95
		-30	24	-16	15	3.67
Superior posterior parietal cortex	L	-28	-68	58	80	4.79
		-42	-66	52	16	4.14
Superior temporal cortex	R	64	4	-10	14	3.90
Inferior temporal cortex	L	-54	-46	-24	19	3.80
Caudate nucleus	R	26	22	12	34	3.83

R = right; L = left; BSR = bootstrap ratio.

Table 2.

Brain regions (from LV1) positively associated to the successful retrieval of self-related items (self_hits vs other_hits) in AD patients.

Lag	Region	Side	MNI coordinates			Cluster size	BSR
			x	y	z		
1	Cerebellum	R	14	-44	-38	70	-4.79
2	Posterior cingulate cortex	M	2	-32	32	17	-4.18
	Hippocampus	L	-22	-20	-20	10	-3.69
	Inferior frontal gyrus	L	-44	4	22	78	-5.85
	Superior anterior parietal cortex	R	38	-50	54	16	-3.62
	Occipital cortex	L	-30	-96	-4	12	-5.42
3	Cerebellum	L	-12	-44	-42	59	-4.69

R = right; L = left; M = median; BSR = bootstrap ratio. Only peak BSR between lag 1 and lag 3 are reported.