

Manuscript title:

Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks

Running title:

Brain networks, hippocampus and memory in dementia

Renaud La Joie^{a,b,c,d,1}, Brigitte Landeau^{a,b,c,d}, Audrey Perrotin^{a,b,c,d}, Alexandre Bejanin^{a,b,c,d}, Stéphanie Egret^{a,b,c,d}, Alice Pélerin^{a,b,c,d}, Florence Mézenge^{a,b,c,d}, Serge Belliard^{a,b,c,e}, Vincent de La Sayette^{a,b,c,f}, Francis Eustache^{a,b,c,d}, Béatrice Desgranges^{a,b,c,d}, Gaël Chételat^{a,b,c,d}

^a INSERM U1077, 14000 Caen, France;

^b Université de Caen Basse-Normandie, UMR-S1077, 14000 Caen, France;

^c Ecole Pratique des Hautes Etudes, UMR-S1077, 14000 Caen, France;

^d CHU de Caen, U1077, 14000 Caen, France;

^e CHU Pontchaillou, Service de Neurologie, 35000 Rennes, France;

^f CHU de Caen, Service de Neurologie, 14000 Caen, France.

¹ **Corresponding author:** Renaud La Joie, Unité U1077, GIP CYCERON, Bd Henri Becquerel – BP 5229, 14074 Caen Cedex, France. Telephone: (+33) 231470173.
Email: lajoie@cyceron.fr

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SUMMARY

Alzheimer's disease (AD) and semantic dementia (SD) are both characterized by severe atrophy in the hippocampus, a brain region underlying episodic memory; paradoxically, episodic memory is relatively preserved in SD. Here we used intrinsic connectivity analyses and showed that the brain networks differentially vulnerable to each disease converge to the hippocampus in the healthy brain. As neurodegeneration is thought to spread within preexisting networks, the common hippocampal atrophy in both diseases is likely due to its location at the crossroad between both vulnerable networks. Yet we showed that in the normal brain, these networks harbor different functions, with episodic memory relying on the AD-vulnerable network only. Overall, disease-associated cognitive deficits seem to reflect the disruption of targeted networks more than atrophy in specific brain regions: in AD, over hippocampal atrophy, episodic memory deficits are likely due to disconnection within a memory-related network.

ETOC/"IN BRIEF" PARAGRAPH

Hippocampal atrophy is associated with severe episodic memory deficits in Alzheimer's disease but not semantic dementia. La Joie et al relate this paradox to the differential impairment of partly overlapping but functionally different large-scale networks that both involve the hippocampus.

RESEARCH HIGHLIGHTS

- Hippocampal atrophy is severe in both Alzheimer's disease and semantic dementia
- In the normal brain, the hippocampus is connected to AD and SD vulnerable regions
- Hippocampal connectivity is related to episodic memory only within the AD network
- This likely explains the preservation of episodic memory in SD

INTRODUCTION

In addition to their relevance as diagnosis and monitoring biomarkers for neurodegenerative diseases, neuroimaging techniques can also be used to further our understanding of the pathophysiological mechanisms of these disorders. Recently, neuroimaging evidences have stressed the interest of studying large-scale networks (Buckner et al., 2005; Pievani et al., 2011), identifiable using resting-state functional magnetic resonance imaging (rs-fMRI) as sets of distant brain areas showing synchronized spontaneous activity, referred to as “functional” or “intrinsic” connectivity (Biswal et al., 1995; Buckner et al., 2013; Van Dijk et al., 2010; Fox and Raichle, 2007; Greicius et al., 2003). Thus, Seeley and colleagues showed that the most vulnerable brain regions in five neurodegenerative diseases corresponded to five distinct intrinsic connectivity networks evidenced in healthy subjects (Seeley et al., 2009). Taking this idea further, it is likely that the cognitive deficits associated with each neurodegenerative disease, and even the variability of clinical phenotypes in a given disease (Lehmann et al., 2013) would correspond to the physiological function of the targeted networks.

Yet, while the emphasis of previous studies was on the distinction between the brain networks targeted by different neurodegenerative diseases, it is to note that in some cases, patterns of disease-associated degeneration substantially overlap. One of the most representative examples is the comparison between Alzheimer’s disease (AD) and semantic dementia (SD), two clinically distinct syndromes. Semantic dementia (Neary et al., 1998), also referred to as the semantic variant of primary progressive aphasia (Gorno-Tempini et al., 2011) or temporal variant of fronto-temporal lobar degeneration (Seeley et al., 2005), is characterized by a gradual and modality-independent loss of semantic knowledge, resulting in specific language disturbances

with impaired naming and word comprehension but a fluent and grammatically correct speech.

Neuroimaging studies showed that, in both diseases, the medial temporal lobe undergoes atrophy (Chan et al., 2001; Galton et al., 2001; Nestor et al., 2006; Schroeter and Neumann, 2011; Duval et al., 2012; La Joie et al., 2012) and hypometabolism (Desgranges et al., 2007; Rabinovici et al., 2008; Mosconi et al., 2005; Nestor et al., 2006; Duval et al., 2012; La Joie et al., 2012). This has been highlighted as a paradox given the widely documented relationship between hippocampal impairment and early episodic memory deficits in AD (Deweert et al., 1995; Köhler et al., 1998; Laakso et al., 2000; Scheltens et al., 1992; Chetelat et al., 2003) faced to the relative preservation of day-to-day episodic memory in SD (Chan et al., 2001; Galton et al., 2001; Nestor et al., 2006; Pleizier et al., 2012). Previous authors have therefore proposed that, beyond the hippocampus, episodic memory impairment in AD would be due to the dysfunction of additional episodic memory-related regions that would be spared in SD (Hornberger and Piguet, 2012; Nestor et al., 2006).

Here, we hypothesized that AD and SD neurodegenerative processes affect the functioning of two different intrinsic networks that preexist in the healthy brain, with the hippocampus being the main “crossroad” between both networks. In addition, we predicted that, in the healthy brain, the role of the hippocampus within these networks would differ, with an involvement in episodic memory function within the AD-targeted network only.

To answer this question, we first highlighted specific functional alteration in each disease using ¹⁸Fluorodeoxyglucose positron emission tomography (FDG-PET) to identify brain areas of greatest cortical metabolism differences between AD and SD.

Then, we revealed the intrinsic connectivity pattern of these regions using rs-fMRI with a seed-based approach in a group of healthy aged subjects. Eventually, we assessed the function of these networks in the healthy brain using correlational analyses between cognitive performances and intrinsic connectivity.

RESULTS

Participants.

Eighteen patients with AD, 13 patients with SD as well as 58 matched controls were included in the present study (Table 1). The comparison of neuropsychological performances between AD and SD patients showed a double dissociation (Chan et al., 2001; Galton et al., 2001; Nestor et al., 2006; Piolino et al., 2003; Pleizier et al., 2012), although both patients groups showed impairment on all tests. SD patients were more severely impaired on semantic memory tasks than AD patients (semantic fluency and picture naming, both $p < 0.01$) while AD patients had lower episodic memory performances (memory subtest from the Mattis dementia rating scale; Lucas et al., 1998; $p < 0.05$). Complementary neuropsychological data are available in Table S1. Overall, this double dissociation supports the idea that these syndromes are characterized by the impairment of two (at least partly) distinct networks.

Comparison of FDG-PET brain metabolism: AD versus SD patients.

The direct voxelwise comparison of glucose metabolism between AD and SD patients revealed significant differences in both directions (Figure 1A and Table 2). Metabolism was significantly lower in SD than AD in bilateral anterior temporal areas, bilateral subgenual and right anterior cingulate cortex (Figure 1A, clusters 1 to

4, orange color scale) while significant reduction in AD versus SD was found in the bilateral precuneus/posterior cingulate cortex and the right angular gyrus (Figure 1A, clusters 5 and 6, blue color scale).

The mean metabolism of AD and SD patients in each of these clusters (where both patient groups significantly differed from each other) was then compared to that of a subsample (n=38) of the healthy control group who had undergone an FDG-PET scan (Figure 1B). Metabolism in the two clusters showing significant reduction in AD versus SD (precuneus/posterior cingulate cortex and right angular gyrus) was specifically altered in AD relative to controls, as SD patients showed no significant difference from controls (all p-values>0.2). Three out of the four clusters showing significant reduction in SD versus AD were specifically altered in SD relative to controls but showed no significant change in AD relative to controls. In the last cluster (the left anterior temporal region; Figure1, cluster 1), significant hypometabolism was observed in AD patients (8.8% reduction as compared to controls; p=0.008) but this difference was subtle as compared to the dramatic decrease in SD (42.5% reduction; $p<10^{-4}$) (Figure 1B, cluster 1).

Intrinsic connectivity in the healthy brain (rs-fMRI).

All AD- and SD- specific regions are intrinsically connected to the hippocampus in the healthy brain.

Using seeds derived from the 6 peaks of metabolism differences between AD and SD patients (see Table 2 for peak coordinates, and Figure 2A), intrinsic connectivity analyses were performed in the group of 58 healthy controls, resulting in 6 intrinsic connectivity maps (Figure 2B). These maps were superimposed to illustrate their overlap and the resulting convergence map indicates the number of overlapping

connectivity maps in each voxel (Figure 2C). Interestingly, the only area included in all 6 connectivity maps was located in the right anterior hippocampus (42 voxels, 336 mm³, MNI coordinates of the center of mass: 24, -16, -22; see Figure 2C, bottom).

Complementary analysis of the structural MRI data obtained in the same patients showed that this “crossroad” hippocampal cluster was located in an area where both AD and SD patients harbor severe gray matter atrophy as compared to controls (Figure 3C).

The relationships between hippocampal intrinsic connectivity and cognitive abilities vary across networks.

Correlations were assessed in the 58 healthy controls between i) individual values of intrinsic connectivity between the crossroad hippocampal cluster and each of the six patient-derived seeds and ii) four cognitive composite scores (episodic memory, verbal knowledge, executive functions and processing speed, see Experimental Procedures for further details). Significant correlations were found between the episodic memory composite score and connectivity between the crossroad hippocampal cluster and the two AD-derived seeds (the precuneus and the right angular gyrus) but none of the four SD-derived seeds (Table 3). There was no significant correlation with any other composite score, indicating that the correlation between episodic memory and hippocampal connectivity with AD-derived seeds was domain-specific.

The variation of intrinsic connectivity along the grand axis of the hippocampus mimics the differential topography of brain hypometabolism in AD versus SD.

Previous studies conducted in humans as well as animal models have highlighted variations in the connectivity of the hippocampus along its anterior-posterior axis

(Aggleton, 2012; Libby et al., 2012; Poppenk et al., 2013). This differential connectivity is thought to have a role in the differences found between disorders that preferentially affect the anterior versus the posterior hippocampus (Park et al., 2013; Small et al., 2011). Interestingly, while the degree of hippocampal atrophy is overall similar in AD and SD, the pattern differs across the anterior-posterior axis, with a stronger predominance of atrophy in the anterior hippocampus in SD patients (Chan et al., 2001; Nestor et al., 2006; see La Joie et al., 2013 for a study comparing the AD and SD patients from the present study). We therefore conducted complementary analysis to assess the differences in anterior versus posterior hippocampal connectivity in the normal brain and how it relates to differences between AD- and SD-related patterns of cortical dysfunction. Anterior and posterior hippocampus seeds were manually delineated (Figure 4A, see also SI Experimental Procedures) and differences in intrinsic connectivity were assessed within the healthy control group (Figure 4B). Regions that were significantly more connected to the anterior than to the posterior hippocampus were located in the anterior temporal lobes (temporal poles, amygdala and anterior parts of middle and inferior temporal gyri) and ventro-medial frontal cortex. On the opposite, posterior brain regions (including the posterior cingulate, precuneus and lateral parietal) and the right thalamus were more strongly connected to the posterior than to the anterior hippocampus.

Interestingly, the regions showing stronger connectivity with the anterior than with the posterior hippocampus (Figure 4B) appeared similar to those of greater hypometabolism in SD versus AD (Figure 1A), and reversely. To confirm this observation, we extracted the FDG values from all controls and patients in the regions that showed a differential connectivity between anterior and posterior

hippocampus (Figure 4C). Indeed, pairwise comparisons showed that the cortical regions that are more strongly connected to the anterior hippocampus (blue) were more hypometabolic in SD than in AD (Mann Whitney: $p < 0.001$) while those more connected to the posterior hippocampus (yellow-orange) were more hypometabolic in AD than in SD (Mann Whitney: $p < 0.001$).

DISCUSSION

Here, we showed that cortical regions of greater hypometabolism in AD versus SD or reversely belong to intrinsic networks that all involve the hippocampus in the healthy brain; yet, hippocampal connectivity supports episodic memory function only within the AD-vulnerable network. The brain areas of preeminent hypometabolism in AD (posterior association cortices) or in SD (anterior temporal and cingulate cortex; Figure 1A) are consistent with those reported in a previous comparable study (Drzezga et al., 2008). Interestingly, we also showed that these differential metabolic alterations mirror the differences in intrinsic connectivity along the anterior-posterior axis of the hippocampus, consistent with the idea that lesions located in the anterior or posterior hippocampus are accompanied with distinct cortical deficits (Park et al., 2013).

The unique contribution of the present study was to identify the hippocampus as a crossroad between AD and SD targeted networks by seeding these disease-specific regions in a group of healthy subjects. Moreover, the present study helps understanding the differential impairment of episodic memory in AD versus SD despite quantitatively comparable hippocampal atrophy. Thus, the role of the connectivity between the hippocampus and AD-, but not SD-vulnerable regions in episodic memory at least partly explains this apparent paradox.

The hippocampus as a crossroad between AD- and SD-targeted networks.

The hippocampus is known to be atrophied and hypometabolic in both AD and SD (Nestor et al., 2006; Schroeter and Neumann, 2011; La Joie et al., 2013 and Figure 3; see also Duval et al., 2012 and La Joie et al., 2012 for additional evidences of atrophy and hypometabolism in the AD and SD patients included in the present study). The present observation that the hippocampus is intrinsically connected to AD and SD-derived regions is in line with the idea that neurodegenerative processes impair preexisting brain networks (Seeley et al., 2009) and progress through transneuronal spread (Zhou et al., 2012). Yet, the finding that the hippocampus belongs to both AD and SD-vulnerable networks differs from the seminal work by Seeley and colleagues, who highlighted the hippocampus as included in the SD-vulnerable network only (Seeley et al., 2009). In a subsequent study, the same group (Zhou et al., 2012) studied “epicenters”, ie regions which connectivity pattern in the healthy brain closely overlaps with disease-associated atrophy patterns and that could constitute key steps for transneuronal spreading of pathology within the corresponding networks. Intriguingly, medial temporal lobe structures (not including the hippocampus itself though) were found to be an *epicenter* of SD, but not of AD. This result was surprising given the well known early hippocampal atrophy (Tondelli et al., 2012), and hypometabolism (Mosconi et al., 2008) in AD as well as neuropathological evidences. Indeed, neurofibrillary tangles, a key pathological landmark of AD, develop in the medial temporal lobe and then spread to the rest of the cortex, probably along anatomical circuits (de Calignon et al., 2012), following a defined pattern (Braak and Braak, 1991; Delacourte et al., 1999). The discordance between the present study and previous ones (Seeley et al., 2009; Zhou et al., 2012)

may reflect methodological and/or sample specificities. Thus, disease-specific regions were identified here by directly comparing both patient groups to each other (versus compared to controls), FDG-PET data were used to define the seeds (instead of structural MRI data) and we used as many seeds as significant clusters in the FDG-PET group comparison analyses (versus one single seed per disease group). Lastly and importantly, the AD patients from Seeley and colleagues were younger (60.4 ± 6.3 years) than in the present study (68.8 ± 8.6 , $t\text{-value}=3.66$, $p < 0.001$). This likely accounts for parts of the discrepancies as early-onset AD patients show less hippocampal and more posterior cortical structural (Frisoni et al., 2007) and metabolic (Rabinovici et al., 2010) alterations, as compared to more typical late-onset AD patients.

Alzheimer's disease, semantic dementia and large-scale networks.

Interestingly, while the different seeds were defined in a data-driven manner with no a priori hypothesis on targeted networks, it is to note that connectivity maps from the two AD-derived seeds (seeds 5 and 6 in Figure 2B) as well as from two of the SD-derived seeds (seeds 2 and 4 in Figure 2B) appeared to match the topography of the default mode network (DMN). This network, which has been a center of attention for more than a decade (Raichle et al., 2001), has been proposed to be especially vulnerable to AD pathophysiological processes (Buckner et al., 2005). For example, high levels of β -amyloid deposition are mainly found in regions of the DMN (Buckner et al., 2009; Jagust and Mormino, 2011). Yet, consistent with the mismatch between the patterns of β -amyloid deposition and neurodegeneration in AD (La Joie et al., 2012), cortical atrophy and hypometabolism are not usually found throughout the whole DMN but more specifically in the posterior DMN regions (Acosta-Cabronero et

al., 2010; Buckner et al., 2005; Lehmann et al., 2013; see also Figure 1A and Figure 3A), at least in early stages. On the opposite, the anterior cingulate and temporal pole, that are also considered as DMN nodes (Andrews-Hanna et al., 2010; Buckner et al., 2005; Damoiseaux et al., 2012; Pascual et al., 2013), are more typically impaired in SD than in AD (Figure 1A; see also Drzezga et al., 2008). This finding echoes other recent studies conducted in SD that showed abnormalities in some nodes of the DMN using either rs-fMRI (Farb et al., 2013; Guo et al., 2013) or task-related fMRI (Frings et al., 2010). While both AD and SD groups show abnormalities in the DMN, it does not necessarily contradict the idea that each neurodegenerative disease targets a specific intrinsic network. Indeed, more recent studies have shown that the DMN is not homogenous but can be fractioned into sub-networks or 'components' in the healthy brain (Andrews-Hanna et al., 2010; Damoiseaux et al., 2012). Our results therefore support such a parcellation of the DMN, showing that different neurodegenerative processes can preferentially target the posterior versus the anterior components of the DMN.

Lastly, the finding that anterior DMN regions are impaired in SD does not imply that this network is necessarily the primary target of SD pathology. Indeed, two intrinsic connectivity networks obtained from SD-derived seeds (bilateral subgenual and perirhinal; Figure 2B) corresponded to different, more localized networks that have been previously described (Biswal et al., 2010; Laird et al., 2011). These two connectivity maps are fully consistent with those reported in previous studies seeding the same regions (for perirhinal, see Kahn et al., 2008 and Libby et al., 2012; for subgenual, see Margulies et al., 2007 and Yu et al., 2011). Interestingly, both networks include anterior DMN nodes (the anterior temporal cortex and the anterior cingulate cortex, see Figure 2B). It is thus possible that, in SD, the pathology

starts in one of these more localized networks and then extends to the anterior DMN through shared nodes, in line with the idea that pathological processes can spread from the initially-targeted network to closely connected networks (Zhou et al., 2012).

Two functionally distinct hippocampal networks in the healthy brain.

In the present work, we also assessed the cognitive correlates of intrinsic connectivity within disease-vulnerable networks. In AD, a posterior network including the precuneus/posterior cingulate, the angular gyrus and the hippocampus showed both hypometabolism (Figure 1) and atrophy (Figure 3A). Correlation analyses showed that hippocampal connectivity within this AD-vulnerable network underlies episodic memory abilities in the healthy brain (Table 3), consistent with the major episodic memory deficits in AD. On the opposite, hippocampal connectivity within the SD-vulnerable network, which includes the temporal poles, medial temporal lobes (including the hippocampi), subgenual and anterior cingulate cortex, does not seem to be related to episodic memory abilities. The present study is consistent with the hypothesis that AD-related episodic memory impairment is due to the dysfunction of an integrated network rather than to focal hippocampal damage, and that this network is globally spared in SD (Nestor et al., 2006). Our findings further highlight the importance of hippocampal connectivity within this network for episodic memory integrity. Thus, while the hippocampus is at the crossroad between AD- and SD-targeted networks, atrophy of this structure is accompanied by major episodic memory impairment in AD (Nestor et al., 2006; Pleizier et al., 2012), but not in SD (Hornberger and Piguet, 2012; Pleizier et al., 2012) because these networks have different cognitive functions.

This observation fits well with the recent proposal that the hippocampus is involved in two cortical systems that harbor different cognitive/memory functions (Ranganath and Ritchey, 2012). On the one hand, the so-called “posterior medial system”, including the posterior cingulate, precuneus and lateral parietal cortex (all part of the AD-derived network in the present study), would notably support episodic memory. On the other hand, the “anterior-temporal system”, including the perirhinal and temporo-polar cortex (both part of the SD-derived network in the present study), would support different aspects of cognition including familiarity-based recognition, social cognition, semantic knowledge representation and emotional processing (Ranganath and Ritchey, 2012). The authors predicted that SD would mainly affect the anterior temporal system consistently with the disproportionate atrophy of the anterior hippocampus in SD (Chan et al., 2001; Nestor et al., 2006). Indeed brain regions of the anterior temporal system are particularly connected to the anterior hippocampus while the posterior medial system would be preferentially related to the posterior hippocampus (Aggleton, 2012; Kahn et al., 2008; Poppenk et al., 2013). This differential alteration of the two hippocampal systems and especially the relative preservation of the posterior medial system in SD would in turn explain the relative preservation of episodic memory in SD. Our data support this hypothesis as we showed (Figure 5) that i) AD and SD differentially affect metabolism in posterior medial versus anterior temporal regions, respectively (Figure 1A); ii) all these regions are connected to the hippocampus, consistent with the idea that they form hippocampal-related networks (Figure 2C), iii) only the connectivity within the posterior medial network correlates with episodic memory in the healthy brain (Table 3), emphasizing the different cognitive roles of these hippocampal systems, and iv) there is a strong similarity between regions that are specifically affected in AD versus

SD and regions that are specifically connected with the posterior versus anterior hippocampus, respectively (Figure 4).

Lastly, studies of structural connectivity using diffusion tensor imaging also support the idea of a differential alteration of hippocampus-related networks in both neurodegenerative diseases. In AD, white matter abnormalities were found in the parahippocampal gyrus, posterior cingulum and temporo-parietal regions (Acosta-Cabronero et al., 2010), which connect the medial temporal lobe to posterior association areas including the posterior cingulate cortex. By contrast, white matter disruption in SD was notably observed in the temporal pole and uncinate fasciculus (Acosta-Cabronero et al., 2011) which connect temporal and frontal cortical areas.

Future directions.

Further studies are required to provide a fully comprehensive insight on this issue. Notably, it will be of interest to study the differential effects of AD and SD on the intrinsic connectivity of the hippocampus, together with their cognitive correlates. In addition, further investigations are needed to better understand the role of hippocampal connectivity within the SD-targeted network in the normal brain, as no correlation with cognitive performance was found in the present study.

Overall, the present study further emphasizes the utility of intrinsic network-based approaches to help understanding the cerebral basis of neurodegenerative diseases and associated cognitive impairments. Previous studies demonstrated that these methods allow defining large-scale networks in the healthy brain that would show selective vulnerability to different neurodegenerative diseases. Here, we showed that two pathological processes can target the same brain region through the impairment

of two functionally distinct but partly overlapping intrinsic networks, therefore resulting in different cognitive deficits.

EXPERIMENTAL PROCEDURES

Participants

All participants were included in the IMAP study (Caen, France) and part of them were included in previous publications from our lab (Arenaza-Urquijo et al., 2013; Duval et al., 2012; La Joie et al., 2012, 2013; Mevel et al., 2013). They were all right-handed, had at least 7 years of education and had no history of alcoholism, drug abuse, head trauma or psychiatric disorder. The IMAP Study was approved by a regional ethics committee (*Comité de Protection des Personnes Nord-Ouest III*) and is registered with ClinicalTrials.gov (number NCT01638949). All participants gave written informed consent to the study prior to the investigation.

Patients were recruited from local memory clinics and selected according to corresponding internationally agreed criteria. Clinical diagnosis was assigned by consensus under the supervision of senior neurologists (VdIS, SB) and neuropsychologists (AP, SE). Briefly, 18 patients with AD fulfilled standard National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical criteria for probable Alzheimer's disease (McKhann et al., 1984). In addition to these clinical criteria, all AD patients underwent a Florbetapir-PET scan and were found to be amyloid-positive using previously published methods (La Joie et al., 2012), therefore increasing the likelihood of genuine AD etiology (Dubois et al., 2010; McKhann et al., 2011). Thirteen patients with SD were selected on the basis of research criteria established by Neary et al. (Neary et al., 1998), with semantic

memory deficits as the predominant and inaugural symptom as reflected by anomia, word comprehension difficulties, semantic paraphasias, prosopagnosia and/or associative agnosia. Florbetapir-PET scans were not acquired in SD patients but as previous studies showed rare amyloid-beta deposition in clinically diagnosed SD patients (Drzezga et al., 2008; Rabinovici et al., 2008; Hodges et al., 2010; Leyton et al., 2011), it is very unlikely that the potential inclusion of a few amyloid-beta positive SD patients had a significant impact on the results.

Lastly, 58 healthy controls were recruited from the community and performed in the normal range on all neuropsychological tests from a cognitive battery assessing multiple domains of cognition (verbal and visual episodic memory, semantic memory, language skills, executive functions, visuo-spatial functions and praxis).

Imaging data acquisition

All participants were scanned on the same MRI and PET cameras at the Cyceron center (Caen, France): A Philips (Eindhoven, The Netherlands) Achieva 3.0 T scanner and a Discovery RX VCT 64 PET-CT device (General Electric Healthcare) respectively. Details on the acquisition procedures are provided in the supplemental experimental procedure.

Structural MRI data processing and analyses

Using the VBM5.1 toolbox, implemented in the SPM5 software (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK), T1-MRI were segmented, spatially normalized to the Montreal Neurological Institute (MNI) space, modulated to correct for non-linear warping effects and smoothed using a 10 mm full-width at half-maximum (FWHM) Gaussian kernel. Both patient groups were compared to the group of 58 healthy controls using a FWE $p < 0.05$ threshold together with a cluster extent $k > 100$ voxels (800 mm^3), including age, sex and

education as covariates. The conjunction of both AD and SD patterns of atrophy was computed with SPM (Nichols et al., 2005).

FDG-PET data processing and analyses

Data pre-processing.

PET data were first corrected for partial volume effects using the three-compartment method described by Giovacchini et al. (2004) and implemented in the PMOD software (PMOD Technologies Ltd., Adliswil, Switzerland). This method uses gray matter, white matter and cerebro-spinal fluid segments obtained from the VBM procedure to correct for both spill-in and spill-out effects. Resultant images were then coregistered onto corresponding MRI, normalized using the deformation parameters defined from the VBM procedure performed on the corresponding MRI and scaled using the mean PET value of the cerebellar grey matter. Resultant images were finally smoothed using a 10 mm FWHM Gaussian kernel.

Statistical analyses.

To compare brain metabolism between AD and SD patients, corresponding images were analyzed with SPM5 using the “two-sample t-test” routine, including age, gender and years of education as covariates. A family-wise error (FWE)-corrected $p < 0.05$ threshold was used, together with a cluster extent $k > 100$ voxels (800 mm^3). To assess the specificity of resulting metabolic defects in both patient groups, individual values of FDG uptake were extracted from each cluster in each patient as well as in the 38 healthy controls who had an FDG-PET scan; pairwise comparisons between the three groups were assessed using non parametric Mann-Whitney tests.

Resting-state functional MRI

Data pre-processing.

Data were pre-processed and spatially normalized using a technique designed to reduce geometric distortion effects (Mevel et al., 2013; Villain et al., 2010) and described in the supplemental experimental procedure.

Intrinsic connectivity analyses in the healthy controls using seeds obtained from the FDG-PET comparison between AD and SD patients.

Using the MarsBar toolbox, we created six 6-mm radius spherical seeds centered on the main peak of each of the 6 significant clusters from the previous comparison of brain metabolism between AD and SD patients (see Table 2 for coordinates). For each of the 58 healthy controls and each seed of interest, positive correlations were assessed between the mean time course in the seed and the time course of each grey matter voxel. To remove potential sources of spurious variance, the time courses from white matter, cerebro-spinal fluid, the whole brain, their derivatives and the 6 movements parameters generated from realignment of head motion were introduced as covariates. A Fisher's z-transform, as well as a 4.5 mm FWHM smooth were finally applied to the individual connectivity maps, resulting in a final smoothness of 6 mm FWHM ($\sqrt{4^2 + 4.5^2}$). For each seed of interest, the 58 individual functional connectivity maps were entered in a one-sample t-test using SPM in order to highlight their brain pattern at a group-level. A statistical threshold of $p(\text{uncorrected}) < 0.001$ and cluster extent $k > 29$ voxels (232 mm^3) was used to achieve a corrected statistical significance of $p < 0.05$, determined by Monte-Carlo simulation (see program AlphaSim by D. Ward).

In order to assess the potential overlap between the connectivity maps derived from the 6 seeds of interest, the 6 SPM-T maps from the one-sample t-tests were thresholded as indicated above, binarized and summed, resulting in a so-called "convergence" map that indicated the number of significant connectivity maps each

voxel belonged to (minimal value = 0 for voxels that are functionally connected to none of the seed regions; maximal value = 6 for voxels that are functionally connected to all 6 seed regions).

Correlations between connectivity and cognition in the healthy controls.

To assess the link between functional connectivity and cognition, we extracted, for each healthy subject, the values of intrinsic connectivity between the crossroad hippocampal cluster (see Figure 2C) and each of the 6 patient-derived seeds (see Figure 2A). We then assessed the correlations between each of these values and cognitive measures obtained from a detailed standardized neuropsychological battery. This cognitive assessment was obtained within a few days or weeks from the functional MRI acquisition. To obtain more robust proxies of cognitive abilities and minimize the issue of multiple statistical testing, four composite cognitive scores were computed. For that purpose, performances from different tasks that showed neither ceiling nor floor effects were Z-transformed and combined as follows (note that before averaging, Z-scores derived from reaction times were reversed so that increasing values always indicated better performances). An *episodic memory retrieval score* was derived from two tests that were previously developed in our lab and based on the ESR (Encoding, Storage, Retrieval) paradigm to assess different processes of episodic memory (Chételat et al., 2003; Eustache et al., 1998; Fouquet et al., 2012). The two scores we used were complementary as the first one was based on a list of 16 words (verbal episodic memory) and the second one was based on a list of 8 non-figurative graphic signs (visual episodic memory) (Mevel et al., 2013). In both tests, we used the performance of free recall for items that had been deeply and intentionally encoded as a proxy for retrieval abilities. A *processing speed score* included i) the time to perform the Trail Making Test (TMT) part A, ii) the

time to complete the word card from the Stroop test (reading color names presented in black ink) and iii) the time to complete the color card from the Stroop test (naming colors presented as rectangles). The *executive function score* combined performances from i) the TMT test (time difference between TMT part B and part A), ii) the Stroop test (time difference between the interference and color cards), iii) the phonemic verbal fluency (number of words beginning with “p” in 2 min). Lastly, a *verbal knowledge score* included i) the semantic verbal fluency (number of animals in 2 min) and ii) the number of correct responses in the Mill Hill Vocabulary test.

Partial correlation analyses were conducted in the healthy control group between the 6 functional connectivity values and the 4 cognitive composite scores, controlling for age, gender and education.

Intrinsic connectivity analyses along the long axis of the hippocampus.

To assess differences in intrinsic connectivity along the long (ie anterior-posterior) axis of the hippocampus, we manually delineated two bilateral regions of interest (ROIs) on the group template (see Figure 4A): one covering the head of the hippocampus (« anterior hippocampus ») and the other covering most of the body of the hippocampus (« posterior hippocampus »), leaving a gap of three unlabeled slices between the two ROIs to limit signal contamination due to spatial smoothing. Note that the most posterior part of the hippocampus (the tail) was not considered because it usually shows poor registration across individuals after spatial normalization (Krishnan et al., 2006; Mosconi et al., 2005). We then used each ROI as a seed and computed maps of intrinsic connectivity in the group of 58 healthy controls (see the “Intrinsic connectivity analyses in the healthy controls using seeds obtained from the FDG-PET comparison between AD and SD patients” paragraph above). To assess the differences of connectivity between anterior and posterior

hippocampal seeds, the resulting two sets of 58 connectivity maps were compared using the “paired t-test” routine in the SPM software.

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Table 1. Demographic information and selected neuropsychological scores.

	HC (n=58)	AD (n=18)	SD (n=13)	Group comparisons ^a	Missing data
Age	64.8 ± 8.7	68.8 ± 8.6	66.2 ± 5.5	ns	
Females: n (%)	31 (53%)	11 (61%)	8 (62%)	ns	
Years of education	12.1 ± 3.4	10.7 ± 3.9	11.4 ± 4.0	ns	
MMSE (/30)	29.2 ± 0.8	21.1 ± 4.0	-	HC>AD***	1 HC, all SD
Mattis total score (/144)	140.5 ± 9.0	115.8 ± 18.4	118.7 ± 8.6	HC>AD***, HC>SD***	1 HC, 3 AD
Mattis memory subtest (/25)	24.5 ± 0.8	15.1 ± 3.8	18.6 ± 4.4	HC>AD***, HC>SD***, SD>AD*	1 HC, 3 AD
Semantic fluency (animals, 2min)	33.6 ± 9.5	16.2 ± 8.2	9.3 ± 3.4	HC>AD***, HC>SD***, AD>SD**	1 HC, 1SD
Picture naming (/80)	79.8 ± 0.4	74.3 ± 7.3	34.9 ± 17.5	HC>AD***, HC>SD***, AD>SD***	2 HC, 2 AD

HC: Healthy controls, AD: patients with Alzheimer's disease, SD: patients with semantic dementia, MMSE: Mini-Mental State Examination. Shown are mean ± standard deviation unless specified otherwise.

^a Except for sex ratio (for which Fisher exact test was used), Kruskal-Wallis non-parametric analyses of variance were used (ns: non significant; all $p > 0.2$); when significant (all $p < 0.001$), Mann-Whitney U tests were used for pairwise comparisons; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Additional neuropsychological data are available in Table S1.

Table 2. Peaks of metabolism differences between AD and SD patients.

Cluster number	Cluster size (mm ³)	Main peak					Labeling	Other regions included in the cluster
		Z-value	x	y	z			
SD < AD								
1	22,496	7.26	-34	-10	-34	L perirhinal cortex	L middle and inferior temporal cortex, L temporal pole	
2	3,760	6.07	38	14	-30	R temporal pole	R fusiform gyrus, R inferior temporal cortex	
3	2,016	5.51	-4	21	-14	L subgenual cortex	R subgenual cortex L caudate nucleus	
4	1,064	5.09	4	34	-10	R anterior cingulate	-	
AD < SD								
5	4,280	5.26	2	-66	36	R precuneus	L precuneus R and L posterior cingulate	
6	2,032	4.88	46	-62	38	R angular gyrus	-	

AD: patients with Alzheimer's disease, SD: patients with semantic dementia, L: left, R: right.

Cluster numbers correspond to the numbers in Figure 1. Coordinates (MNI space) are given for the main peak of each significant cluster and were used to make seeds for the intrinsic connectivity analyses (Figure 2A).

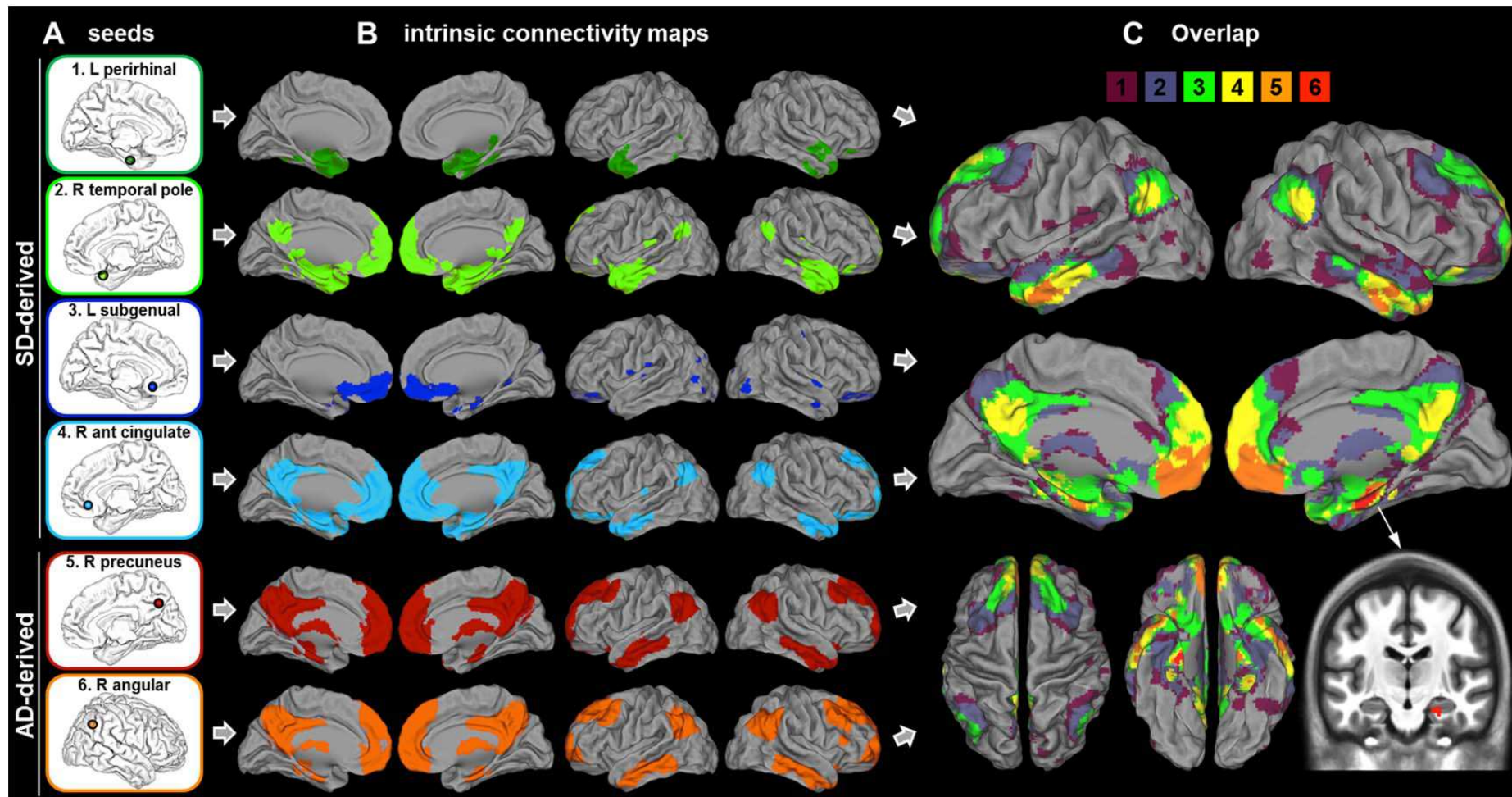
Table 3. Correlations between intrinsic connectivity and cognitive abilities in the healthy controls.

	Resting-state intrinsic connectivity between the crossroad hippocampal cluster and the seed located in:					
	L perirhinal	R temporal pole	L subgenual	R anterior cingulate	R precuneus	R angular
Episodic memory retrieval (n=56) ^a	r = -0.23 p = 0.08	r = 0.10 p = 0.46	r = -0.09 p = 0.53	r = 0.03 p = 0.84	r = 0.41 p = 0.002^b	r = 0.35 p = 0.009
Verbal knowledge (n=54) ^a	r = -0.05 p = 0.73	r = 0.01 p = 0.94	r = -0.18 p = 0.19	r = 0.04 p = 0.80	r = -0.05 p = 0.70	r = 0.05 p = 0.70
Executive functions (n=54) ^a	r = -0.08 p = 0.56	r = 0.14 p = 0.32	r = -0.00 p = 0.98	r = 0.03 p = 0.84	r = 0.23 p = 0.10	r = 0.10 p = 0.49
Processing speed (n=55) ^a	r = 0.19 p = 0.17	r = -0.23 p = 0.10	r = -0.06 p = 0.66	r = -0.18 p = 0.18	r = -0.11 p = 0.40	r = -0.05 p = 0.72

r-values correspond to partial correlation coefficients, controlling for age, gender and years of education. Significant correlations ($p < 0.05$) are bolded. ^a Data were missing for a few healthy controls. ^b The correlation remained significant when using a stringent Bonferroni correction ($\alpha = 0.05 / 24 = 0.0021$).

Corresponding scatterplots are available in Figure S2 together with additional statistical information about the distribution of the different variables.

Figure 2. Intrinsic connectivity maps derived from AD- and SD-specific seeds converge in the hippocampus.



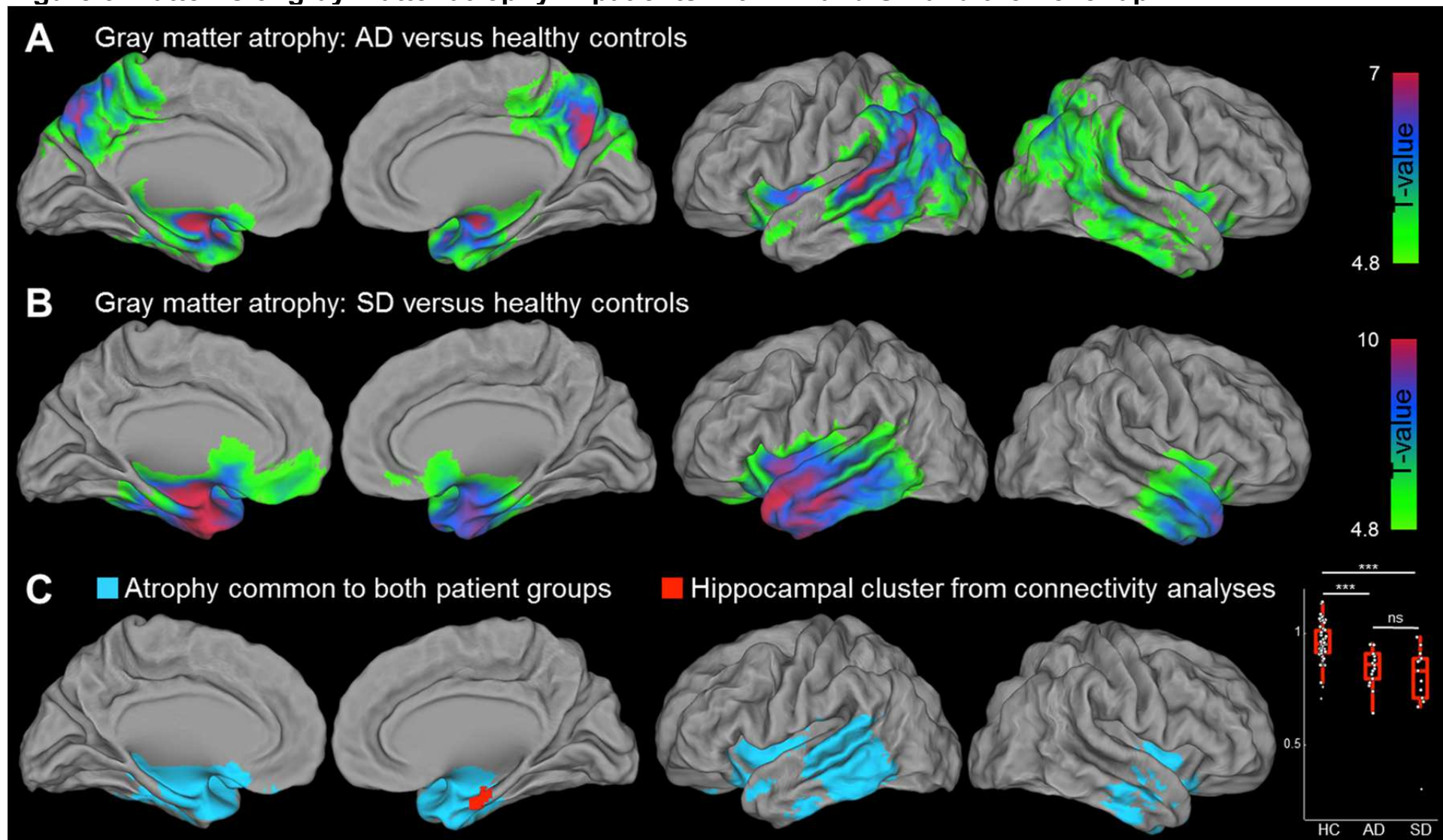
Results of the seed-based intrinsic connectivity analyses performed within the healthy controls using resting-state functional magnetic resonance imaging.

A. The seeds are centered on the peak of each of the 6 clusters where metabolism differed between Alzheimer's disease (AD) and semantic dementia (SD) patients (see Figure 1A and Table 2 for coordinates; seed numbers are consistent between figures).

B. Group-level analyses led to 6 intrinsic connectivity maps.

C. The spatial overlap between these 6 maps was then assessed; the colorbar indicates the number of overlapping connectivity maps in each voxel. The lower-right quadrant shows the only cluster of overlap between the 6 connectivity maps located in the right anterior hippocampus (hereafter referred to as the crossroad hippocampal cluster).

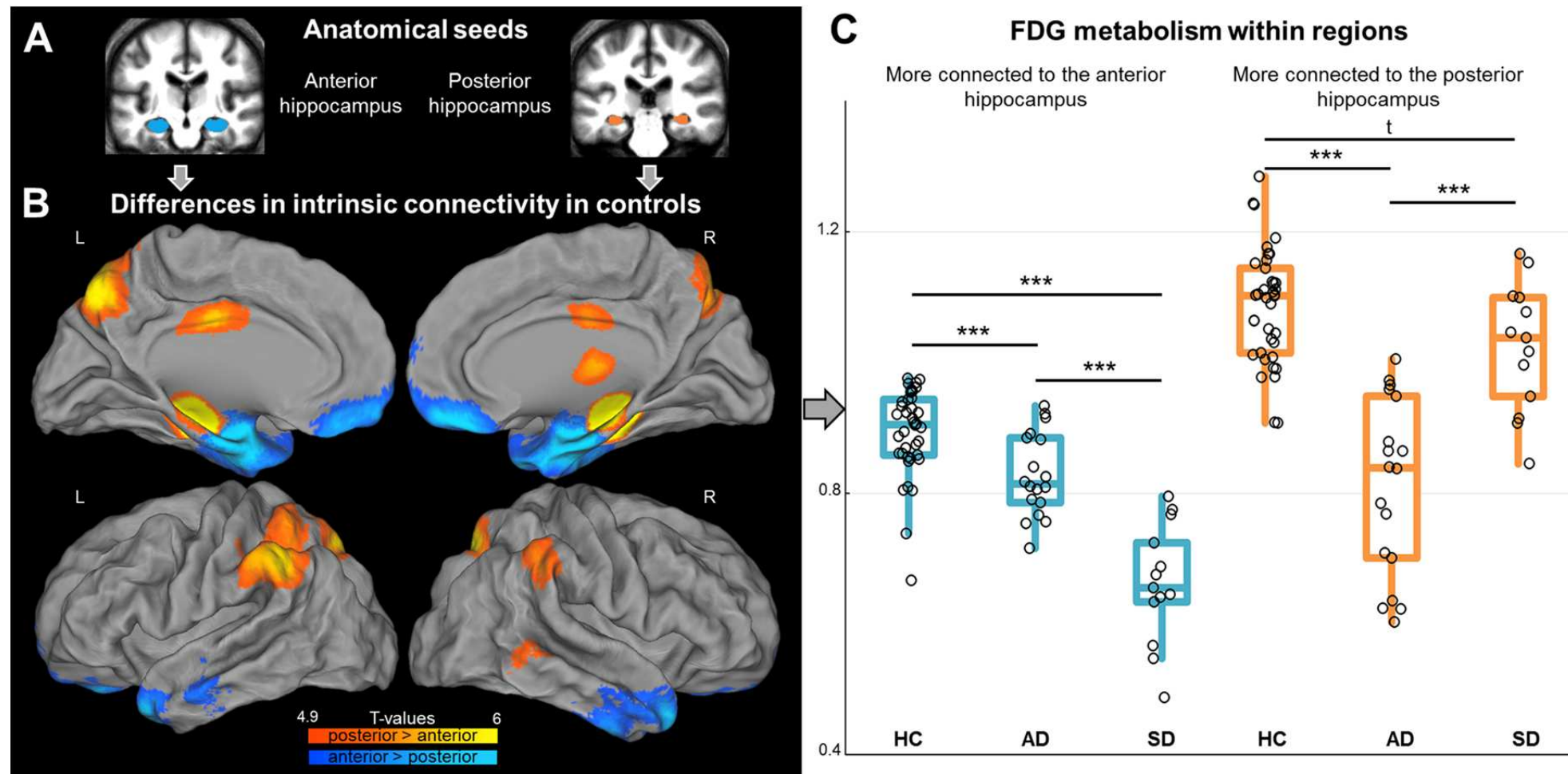
Figure 3. Patterns of gray matter atrophy in patients with AD and SD and their overlap.



A and B. Each patient group was compared to healthy controls. Results are presented using thresholds of FWE-corrected $p < 0.05$ and cluster extent $k > 100$ voxels (800mm^3). Colorscales are adapted to the range of significance for each comparison.

C. The “crossroad” hippocampal cluster (red, also shown in Figure 2C) is located in an area where both AD and SD patients are significantly atrophied as compared to controls (cyan). The mean value of gray matter volume within this crossroad hippocampal cluster was extracted in each individual and plotted on the bottom right quadrant. Pairwise differences were assessed using Mann-Whitney tests; ns: non significant ($p = 0.35$); ***: $p < 0.001$.

Figure 4. Variations of intrinsic connectivity along the grand axis of the hippocampus mirror the differential topography of brain alterations in AD versus SD.

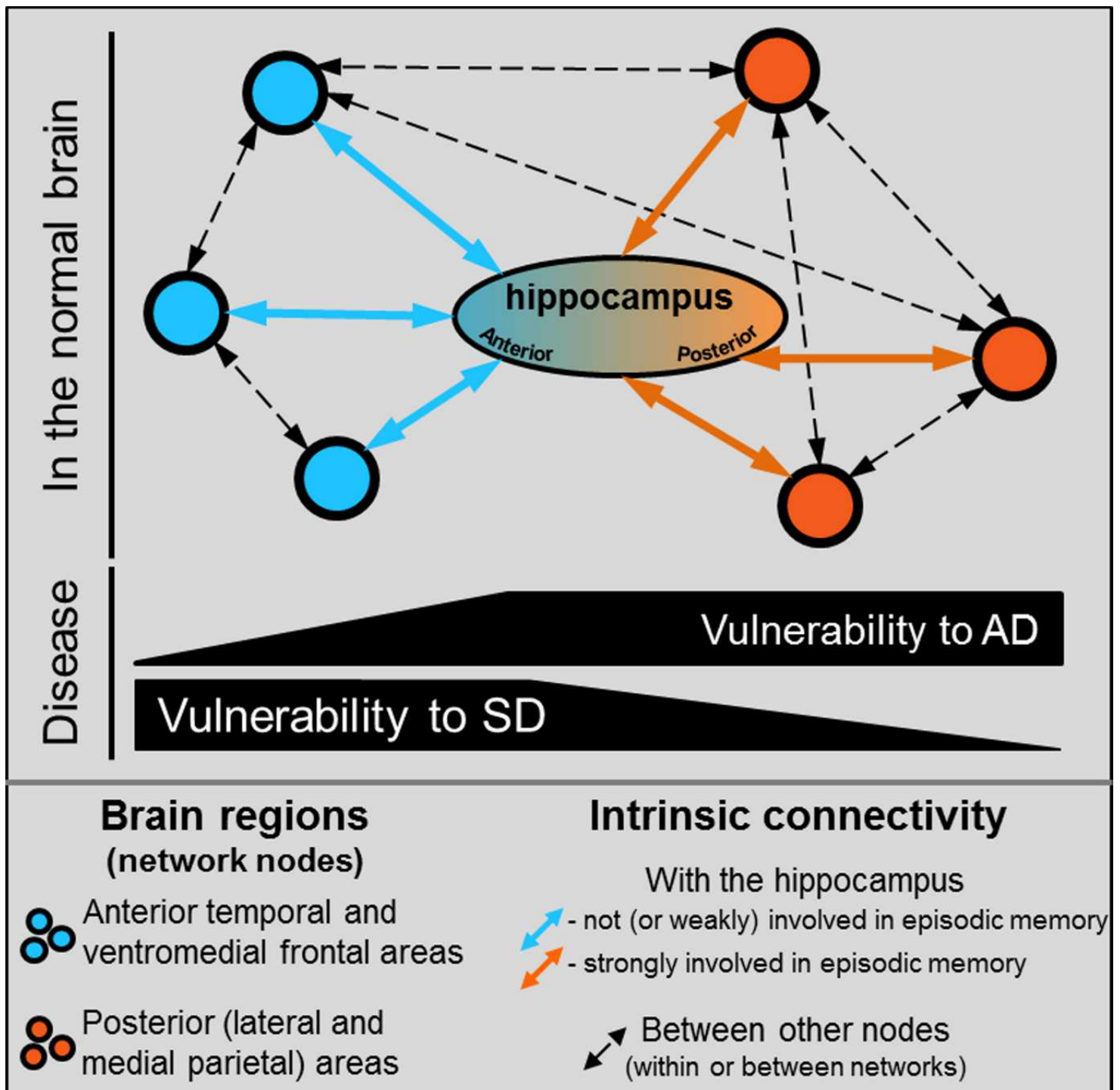


A. Bilateral anterior and posterior hippocampal seeds were manually traced and intrinsic connectivity maps were derived in the group of 58 healthy controls.

B. A voxelwise paired t-test was performed to identify regions that were more connected to the anterior than to the posterior hippocampus (blue), or the opposite (orange).

C. FDG-PET values within these two sets of brain regions for all participants. Pairwise differences were assessed using Mann-Whitney tests; t: trend ($p < 0.10$); ***: $p < 0.001$.

Figure 5. Schematic model summarizing our findings and hypothesis.



In the normal brain, the hippocampus is a main crossroad between two functional brain networks that are differentially involved in episodic memory. These networks are also differentially affected by AD versus SD pathophysiological processes, resulting in distinct vulnerability of episodic memory in these two degenerative diseases despite common hippocampal alteration. Note that, in addition to their connectivity with the hippocampus, some brain regions or 'nodes' show intrinsic connectivity with regions from the same network (e.g. the precuneus and angular cortex) or from the other network (e.g. the anterior cingulate cortex, the precuneus and angular gyrus).