Modulation of the Default-Mode Network Between Rest and Task in Alzheimer’s Disease

Graeme C. Schwindt1,5, Simone Chaudhary2,6, David Crane5,7, Anoop Ganda5, Mario Masellis1,5,8,9, Cheryl L. Grady3,4,10, Bojana Stefanovic2,6 and Sandra E. Black1,5,7,8,10

1Institute of Medical Science, 2Department of Medical Biophysics, 3Department of Psychology, 4Department of Psychiatry, University of Toronto, Ontario, Canada 7L.C. Campbell Cognitive Neurology Research Unit and Brain Sciences Research Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada 8Imaging Research, Sunnybrook Research Institute, Toronto, Ontario, Canada 9Heart and Stroke Foundation Centre for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada 7Division of Neurology, Department of Medicine, Sunnybrook Health Science Centre, University of Toronto, Toronto, Ontario, Canada 9Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada and 10Rotman Research Institute, Baycrest, Toronto, Ontario, Canada

Address correspondence to Graeme Schwindt, Sunnybrook Health Sciences Centre, Room A-421, 2705 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5. Email: graeme.schwindt@utoronto.ca

Default-mode network (DMN) connectivity at rest is disrupted in Alzheimer’s Disease (AD), but it is unknown whether this abnormality is a static feature, or if it varies across cognitive states. We measured DMN integrity in 16 patients with mild AD and 18 controls during resting state and a simple visual task. Patients showed resting-state deficits in the parahippocampal gyrus and posterior cingulate. No group differences were found during the task. Controls exhibited higher DMN connectivity of multiple regions during rest than task, while the patient group showed no modulation of the DMN between states. However, the relative degree of increased resting- versus task-state co-activation in the posterior cingulate and precuneus was predictive of mini-mental status exam (MMSE) scores in AD patients, while measures at rest or task alone were not associated with MMSE. These findings suggest that a resting state may be more suited to detecting DMN abnormalities in AD than a simple task. However, the degree of state-dependent modulation in the DMN may be a better predictor of the individual cognitive status than a single-state acquisition. This study demonstrates an apparent reduction in the capacity for DMN modulation in individuals with mild AD, the degree of which uniquely predicted cognitive status.

Keywords: default-mode network, dementia, functional connectivity, functional MRI, medial temporal lobe

Introduction

There is an urgent push for novel therapeutic interventions in Alzheimer’s Disease (AD) to delay or halt its progression, and an associated need for biomarkers for early detection, differential diagnosis, and to act as surrogate measures in clinical trials (Hampel et al. 2010). A number of imaging methodologies have been applied to this important research goal, including functional magnetic resonance imaging (fMRI; Sperling et al. 2010).

A growing body of work has focused on examining deficits of network connectivity in AD, specifically within the default-mode network (DMN). The term “default mode” describes a set of brain regions that demonstrate reduced activity across a range of tasks requiring external attention, and are therefore most active during periods of relative rest (Shulman et al. 1997; Gusnard and Raichle 2001; Mazoyer et al. 2001). The DMN is now thought to represent one of a number of resting-state networks, which shows intrinsic connectivity (Greicius et al. 2003), may reflect functional systems, and can be elegantly isolated with multivariate techniques (Biswal et al. 1995; Beckmann et al. 2005; Smith et al. 2009). The precise function of the DMN remains unknown. Meta-analyses and experiments lend support to a role in autobiographical and episodic memory (Buckner et al. 2005; Svoboda et al. 2006), self-reference (e.g. Harrison et al. 2008; Grigg and Grady 2010), and spontaneous cognition (Buckner et al. 2008; Andrews-Hanna, Reidel, Huang, et al. 2010).

AD is associated with metabolic decline in areas that overlap nodes of the DMN, including the posterior cingulate and lateral parietal cortices (Mishima et al. 1997; Schroeter et al. 2009). Multiple studies have investigated DMN connectivity in AD, showing abnormalities in intrinsic connectivity (e.g. Greicius et al. 2004; Zhang et al. 2010; Zhou et al. 2010; Binnewijzend et al. forthcoming) and task-induced deactivation patterns (Lustig et al. 2003; Rombouts et al. 2005; Pihlajamäki and Sperling 2009). Other work has demonstrated DMN dysfunction in populations at-risk of AD, including individuals with mild cognitive impairment (MCI) (Sorg et al. 2007), healthy individuals harboring fibrillar amyloid burden (Sperling et al. 2009; Sheline, Morris, et al. 2010; Sheline, Raichle, et al. 2010), and cognitively intact carriers of the high-risk ApoE4 allele (Filippini et al. 2009; Machulda et al. 2011; Westlye et al. 2011). Recent findings indicate that DMN changes may precede the deposition of amyloid in ApoE4 carriers (Sheline, Morris, et al. 2010; Sheline, Raichle, et al. 2010), and further that these changes are not accounted for by structural or perfusion deficits (Filippini et al. 2009). This suggests that altered DMN connectivity may represent a non-invasive marker of early neuronal dysfunction in AD that could precede abnormalities detected with other imaging techniques.

While there is a good reason for enthusiasm about the potential of DMN investigation in AD as a tool for early detection, differential diagnosis (Zhou et al. 2010), and disease tracking (Damoiseaux et al. 2012), there are still unanswered questions about the nature of DMN dysfunction in this disease. A key question is whether it represents an invariant feature at a given stage of AD, akin to hippocampal atrophy or amyloid deposition, or whether it fluctuates across different cognitive states. The majority of recent work has investigated functional connectivity abnormalities in AD during the resting state. These have reported reductions in connectivity of multiple areas, including the posterior cingulate and medial temporal lobe (MTL; Zhang et al. 2010; Zhou et al. 2010; Damoiseaux et al. 2012; Agosta et al. forthcoming; Binnewijzend et al. forthcoming). Other researchers have examined task-induced
deactivation abnormalities, where patients show an aberrant persistence of activation in normally deactivated regions (Lustig et al. 2003; Rombouts et al. 2005; Celone et al. 2006; Pihlajamäki and Sperling 2009). These task findings may also reflect DMN dysfunction, suggesting some consistency across both resting state and activation studies. However, the interpretation of task findings is complicated by the influence of effort and performance on the magnitude of deactivation (McKiernan et al. 2003), which can confound the interpretation of group differences (Gould et al. 2005; Gould, Arroyo, et al. 2006; Gould, Brown, et al. 2006).

There is a growing understanding that the DMN may vary substantially across cognitive states. A number of studies have compared connectivity patterns across various tasks and rest in healthy young populations (Fransson 2006; Fransson and Marrelec 2008; Harrison et al. 2008; Grigg and Grady 2010; Spreng and Grady 2011), and in patients with schizophrenia (Callhoun et al. 2008). These have found evidence for persistent DMN patterns across a range of cognitive tasks, with some changes in connectivity or regional activation depending on the task examined. The DMN thus appears generally robust, but may not be identically instantiated across different settings. It follows that different cognitive states may reveal different patterns of DMN deficiency in AD on the whole, or that a measure of “change” in DMN connectivity between states could provide clinically useful information. This question is of substantial theoretical and practical importance, but cannot be directly addressed from the existing literature.

In the present study, we collected both resting state and task data in a group of mild AD patients and healthy controls. We examined differences in DMN dysfunction detected across these 2 settings, in addition to their ability to predict cognitive status. We equated analytical methods between these 2 data-sets, adopting a dual regression technique (Filippini et al. 2005), which can confound the interpretation of group differences (Gould et al. 2005; Gould, Arroyo, et al. 2006; Gould, Brown, et al. 2006).

Materials and Methods

Participants

All participants gave written consent and the institutional research ethics board approved procedures. Sixteen patients newly diagnosed as mild probable AD by the latest criteria (McKhann et al. 2011) were recruited through the Sunnybrook Dementia study and scanned immediately prior to starting cholinesterase inhibitor treatment. Patients were matched to 18 healthy, community-dwelling volunteers, with no history of neurological or psychiatric diagnoses. See Table 1 for demographic and cognitive measures.

Imaging Procedure

Approximately 2 weeks before scanning, participants underwent a mock session that introduced the task in an approximation of the scanning environment. This familiarized them with the response box, head-coil mirror, and screen, and requirements to minimize head motion. Prior to entering the scanner, they practiced the experimental task, and instructions were reiterated before each task run in the course of the scanning session. Participants rated the difficulty of the task on a 5-point Likert scale immediately after the scan (1 = extremely easy; 5 = extremely difficult).

Table 1

<table>
<thead>
<tr>
<th>Sex</th>
<th>Controls (N = 18)</th>
<th>Patients (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.0 (7.4)</td>
<td>72.2 (9.9)</td>
</tr>
<tr>
<td>Education</td>
<td>16.0 (3.6)</td>
<td>14.4 (3.6)</td>
</tr>
<tr>
<td>MMSE total*</td>
<td>28.6 (6.9)</td>
<td>25.3 (2.0)</td>
</tr>
<tr>
<td>DRS total**</td>
<td>139.8 (2.4)</td>
<td>123.3 (8.5)</td>
</tr>
<tr>
<td>CDR—sum of boxes</td>
<td>NA</td>
<td>3.28 (1.2)</td>
</tr>
</tbody>
</table>

Note: MMSE, mini-mental status examination ( Folstein et al. 1975); DRS, Dementia Rating Scale (Juncia et al. 2001); CDR, Clinical Dementia Rating (Morris 1993); NA, not applicable. All values are mean [standard deviation].

*DRS score was not available for one patient.

Imaging was performed on the 3.0T GE MR-750 Scanner at the Sunnybrook Research Institute. First, a high-resolution 3D T1-weighted image was acquired (Repetition time (TR) 8.1 ms, echo time (TE) 3.1ms, 256 x 192 matrix, 22 cm field of view (FOV), 186 slices of 1 mm thickness), followed by acquisition of the 2 functional task runs [T2*-weighted echoplanar imaging (EPI), TR 2000 ms, TE 30 ms, 64 x 64 matrix, 20 cm FOV, 26 slices of 5 mm thickness, 172 frames]. These task runs were followed by the resting-state acquisition (180 frames). A number of other sequences were subsequently acquired but are not reported here. Task runs always occurred immediately prior to the resting-state run, to keep them close in time to the pre-scan practice session.

Activation Task

The functional activation paradigm was a simple detection task requiring participants to press a button when they noted identical stimuli in succession within a block of 12 sequentially presented images. This is similar to a typical 1-back task design, but requires only one response when a repeated stimulus is noted. Stimuli were grayscale images of houses or faces, each presented for 1500 ms with a 500 ms interstimulus interval, with one repeat randomly placed within each block. Two runs of the activation task were completed, each consisting of 8 task blocks of 12 images interleaved with 16 s blocks of visual fixation, serving as a baseline state during which participants made no responses.

Image Preprocessing

Figure 1 shows an overview of the analytical pipeline. Preprocessing and analysis of imaging data were carried out using the Oxford centre for functional MRI of the brain software library (Smith et al. 2004). T1-weighted volumes were transformed into standard Montreal Neurological Institute (MINI) space using a full affine registration followed by non-linear registration with 10-mm warp resolution. Native space T1-weighted images were segmented into grey matter (GM) partial volume images using FAST 4.1 (Zhang et al. 2001). These GM images were then transformed into the MINI space, smoothed by 8 mm full-width at half-maximum (FWHM), and demeaned across the 2 groups for use as a voxel-wise covariate in subsequent between-group comparisons. EPI volumes for resting state and task runs were reconstructed, motion corrected, and transformed into standard space by applying the transformation from the corresponding high-resolution T1-weighted image. EPI data were spatially smoothed by an 8-mm FWHM Gaussian kernel and high-pass filtered at 100 s (0.01 Hz).

Independent Components Analysis and Dual Regression

Fully pre-processed resting state and task data (run 1) for all participants were entered into temporal concatenation group independent components analysis (ICA) using MELODIC (Beckmann and Smith 2004; Beckmann et al. 2005), with automatic dimensionality estimation. Forty components were identified from this output, including one identified as the DMN. The DMN map consisted of bilateral contributions from medial prefrontal, lateral parietal, dorso-lateral prefrontal, posterior cingulate, precuneus, thalamus, and left MTL regions (Fig. 2).
All components identified from this single group ICA were used for subsequent dual regression of resting and task data for all participants. Dual regression determines individual, voxel-wise measures of integration associated with a network identified spatially at the group level, without requiring specification of a seed region (Filippini et al. 2009). In the first stage of dual regression, the component maps were used as a set of spatial regressors in a general linear model for each subject’s resting and task data series. The output of this first stage produced subject-specific time courses associated with each spatial component. These time courses were then used as temporal regressors in a second regression (stage 2) to determine subject-specific spatial maps associated with the time course of the group-level DMN. This serves to produce subject-specific DMN maps, representing the voxel-wise strength of association with the time course of the DMN identified from the group ICA. This measure is referred to as co-activation, reflecting how well a given voxel displays the overall DMN temporal pattern. Output of dual regression for all patients and controls produced maps representing the voxel-wise strength of co-activation normalized by the residual noise (Z-score) associated with the DMN component in the resting and task states. This was completed for resting and task data using non-parametric estimation with the Randomise tool (http://www.fmrib.ox.ac.uk/fsl/randomise/), with 5000 permutations to generate the null distribution. GM partial volume images were used as a covariate to account for atrophy at the voxel level. Results were thresholded at \( P<0.05 \), corrected for family-wise error (FWE) across the component map mask, and subjected to threshold-free cluster enhancement (Smith and Nichols 2009).

Additionally, to examine the temporal dynamics of the DMN during the task and rest, time courses from the first stage of dual regression were averaged within each group, to produce group average time courses for the DMN. This was done to confirm the expected task-negative pattern of activation during the task runs. Resting time-courses are included for completeness in Supplementary Figure 1. Within-subject contrasts compared DMN co-activation strength between resting and task settings (paired \( t \)-test). Difference images were also produced for each subject from the output of dual regression, and compared between groups to assess differences between patients and controls in the degree of DMN modulation between the 2 states (unpaired \( t \)-test). This interaction effect was examined at a more lenient statistical threshold (\( P<0.005 \), uncorrected). Voxel-wise regression against mini-mental status exam (MMSE) scores in the 16 patients was conducted with resting, task, and difference images to examine regions showing a significant relationship with cognitive status across the DMN map (\( P<0.05 \), FWE-corrected).
Results

Behavioral Data

Both groups performed the task well. Statistics were performed on the behavioral results for all 16 patients and 18 controls. One-way analysis of variance revealed that the groups did not differ in mean number of hits ($F_{1,31} = 2.2, P > 0.1$) or false alarms ($F_{1,31} = 0.8, P > 0.2$). Patients had significantly longer reaction times than controls ($F_{1,31} = 9.1, P = 0.005$). Subjective difficulty ratings were also low, and did not differ between groups ($F_{1,31} = 0.02, P > 0.8$; Table 2).

Imaging Data

Resting DMN

When patient and control groups were compared during the resting state, we found multiple areas with reduced DMN co-activation in patients. These were localized to multiple regions of the posterior midline, including retrosplenial and dorsal posterior cingulate and precuneus, along with the left posterior hippocampus and parahippocampal gyrus (PHG; Fig. 3). When voxel-wise GM density was included as a covariate, only the PHG cluster remained significant. No areas showed increased DMN co-activation among patients compared with controls.

Task DMN

The DMN time course output from the first stage of dual regression showed a task-negative pattern in both patient and control groups, with greatest activation magnitude occurring during fixation blocks (Fig. 4). When DMN maps during the task were compared between groups, no differences were found, with or without a GM covariate. A supplemental analysis using both runs of task data (averaging the co-activation maps across these 2 runs) also failed to find any differences between the 2 groups.

Task versus Rest DMN

Controls. When we compared DMN maps in controls between the resting and task settings, there was significantly higher DMN co-activation in a number of regions during the resting state. These were localized to the posterior cingulate, precuneus, and left PHG. No areas showed higher DMN co-activation during task compared with rest (Fig. 5).

Patients. Patients showed no significant differences in DMN co-activation between task and rest states in either direction.

Controls versus Patients. Difference images of DMN co-activation were compared between groups. At a more lenient statistical threshold ($P < 0.005$ uncorrected), we found a cluster in the left PHG which showed a greater increase in DMN integration during the rest condition among controls compared with patients (Fig. 6A). This cluster remained after controlling for GM density. Patients have no appreciable change in co-activation in this area, while controls show a significant drop from rest to the level of patients during the task (Fig. 6B).

Relationship to MMSE Score in Patients

Voxel-wise regression analyses in the patients revealed no areas showing significant relationships between MMSE score and DMN co-activation at rest or during task, with or without GM correction. Difference images showed clusters in the precuneus and posterior cingulate where a larger relative increase in DMN integration during rest versus task predicted a higher MMSE score. These clusters were increased in extent after GM correction (Fig. 7A). The regression line within these clusters revealed a strong relationship between magnitude of modulation and MMSE score (Fig. 7B).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 18)</th>
<th>Patients (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hits</td>
<td>15.6 (0.7)</td>
<td>15.2 (1.1)</td>
</tr>
<tr>
<td>Number of false alarms</td>
<td>0.5 (0.7)</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>Reaction time (ms)*</td>
<td>693 (95)</td>
<td>798 (104)</td>
</tr>
<tr>
<td>Difficulty rating</td>
<td>1.3 (0.1)</td>
<td>1.3 (0.2)</td>
</tr>
</tbody>
</table>

Note: All values are mean (standard deviation).
* $P < 0.05$ for group comparison.

Figure 3. Patients show reduced DMN co-activation compared with controls during rest ($P < 0.05$, FWE-corrected).
Discussion

Multiple DMN Abnormalities are Seen in AD During Rest

In the resting state, we found significant disruptions of DMN co-activation in AD patients, in agreement with previous work (Greicius et al. 2004; Zhang et al. 2010; Zhou et al. 2010; Agosta et al. forthcoming; Binnewijzend et al. forthcoming). Some, but not all of these differences were shown to be directly related to structural differences in the affected regions. We noted these reductions in DMN connectivity within posterior cingulate, precuneus, and the left PHG. The PHG cluster suggests a leftward bias in MTL degradation with in the DMN, as has been reported in other imaging modalities in AD (Greicius et al. 2004; Schroeter et al. 2009; Schwindt and Black 2009; Zhang et al. 2010). However, we did not have an a priori hypothesis regarding hemispheric differences that would allow a formal test of asymmetry. A post hoc exploratory analysis was done using a standard PHG region of interest in the left and right hemispheres, which did not find any evidence of a true hemispheric asymmetry (see Supplemental Material).

In line with past work (Greicius et al. 2004; Zhang et al. 2010; Damoiseaux et al. 2012; Binnewijzend et al. forthcoming), we found significantly less DMN co-activation within the posterior cingulate and precuneus in AD patients. When atrophy was accounted for, these differences were no longer significant, suggesting that they are largely a consequence of structural differences between groups. Some studies have found more persistent posterior cingulate abnormalities even after controlling for voxel-wise structural differences (Damoiseaux et al. 2012; Agosta et al. forthcoming). It should be noted that our patients were on average at a less severe stage of disease than in these recent reports, judged by mean MMSE scores. To our knowledge, this is also the first DMN study of mild AD patients scanned prior to receiving cholinesterase inhibitor treatment.

No DMN Abnormalities are Seen During Successful Task Completion

We found no areas of difference in DMN co-activation between the groups during task completion. This result is contradictory to some previous task studies of DMN abnormalities in AD, which has found abnormalities in the medial prefrontal cortex and regions of the posterior cingulate and precuneus during task completion (Lustig et al. 2003; Rombouts et al. 2005; Celone et al. 2006; Pihlajamäki and Sperling, 2009). This is likely explained by differences in task design and behavior. We utilized a relatively easy task with minimal demands on episodic or semantic memory. Hence, both patients and controls performed near ceiling (though patients were slower on average), and did not find the task subjectively difficult. Past work has not equated these factors...
across groups, and some studies have reported significantly poorer performance among patients than controls (Lustig et al. 2003; Rombouts et al. 2005). This is relevant given evidence that fMRI is sensitive to such behavioral differences between AD and healthy populations (Gould et al. 2005; Gould, Arroyo, et al. 2006). Indeed, Gould, Brown, et al. (2006) found normal task-induced deactivation among AD patients when they were successfully performing a paired associates learning task. Our results dovetail with these findings: During successful completion of a simple task, patients show normal functional connectivity within the DMN, despite showing resting-state abnormalities.

Our results indicate that rest and task states show conflicting evidence for disrupted DMN function in AD. Left MTL co-activation was reduced in patients during passive rest, in addition to portions of the precuneus and posterior cingulate. While some of this was attributable to structural differences, none of these areas showed disrupted connectivity in the task setting. These findings may fit with work showing that passive rest is associated with spontaneous thought processes and concomitant activation of the MTL (Andreasen et al. 1995; Christoff et al. 2004). Indeed, an MTL subsystem of the DMN may support internally directed thoughts on the past and future (Andrews-Hanna, Reidler, Huang, et al. 2010; Andrews-Hanna, Reidler, Sepulcre, et al. 2010; Spreng and Grady 2011). This putative subnetwork overlaps considerably with the areas of dysfunction noted in our resting-state analysis, including contributions from the PHG and retrosplenial posterior cingulate (Andrews-Hanna, Reidler, Sepulcre, et al. 2010). In the context of AD research, our results imply that patients show abnormalities in this subsystem that are made apparent in the resting state. In contrast, the cyclical nature of the blocked-design task prompts a fundamentally different cognitive set, requiring some degree of vigilance and anticipation even during fixation blocks. This could reduce sensitivity to group differences in MTL territories and associated nodes of this subsystem. The existing literature supports this idea: All studies reporting disrupted MTL-DMN connectivity in AD have used either resting-state acquisitions (Zhang et al. 2010; Zhou et al. 2010) or passive sensory tasks with minimal cognitive demands (Greicius et al. 2004). Studies of task-deactivation, while reporting medial cortical abnormalities, have not reported any differences in MTL signal within the DMN (Lustig et al. 2003; Rombouts et al. 2005; Pihlajamäki and Sperling 2009).

Healthy Controls Modulate the DMN during the Resting State

In explaining the lack of group differences during the task state, within group comparisons were informative. Healthy controls showed a salient increase in DMN co-activation of multiple regions (posterior cingulate, precuneus, and PHG) during the passive resting state when compared with the task setting. In contrast, patients showed no differences in MTL integration across these 2 settings, suggesting a DMN that is comparatively less dynamic in mild AD.

One interpretation of these findings is that healthy controls show increased functional connectivity of this MTL-DMN
subsystem during passive rest when compared with task completion. The regions showing these differences again partially overlap with nodes in this system (Andrews-Hanna, Reidler, Sepulcre, et al. 2010). This change could reflect the sustained focus and attention required for the task, which may attenuate the internally directed episodic processes associated with this portion of the DMN, in contrast to the resting state. While we are careful to avoid reverse inference, and cannot ascertain what mental processes our participants were engaged in, there is some previous work that supports this idea in healthy individuals. Fransson (2006) and Fransson and Marrelec (2008) found greater DMN connectivity in multiple regions, including the posterior cingulate and PHG during a passive resting state when compared with a working memory task. Andrews-Hanna, Reidler, Huang, et al (2010) found a direct relationship between the degree of MTL-DMN connectivity and internally directed episodic thoughts reported by participants. In contrast to this apparent modulation in healthy older controls, patients showed no significant DMN differences across these 2 states. When we directly compared the degree of modulation between groups, controls showed some evidence for a greater increase in the left PHG and hippocampal DMN integration during rest than did patients.

Individuals with even early stage AD may have a more tonically dampened MTL-DMN system regardless of cognitive state, an abnormality partially a consequence of atrophy and functional disconnection within the key components of system (i.e. MTL, posterior cingulate). These results add to the growing literature demonstrating that DMN connectivity patterns are not fixed across different cognitive states. While healthy older adults exhibited this phenomenon, we demonstrate for the first time a lack of modulation in mild AD patients, and highlight the importance of this dissociation for detecting group differences.

**DMN Modulation Uniquely Predicts Cognitive Status**

Voxel-wise regression analyses demonstrated a strong relationship between degree of increase in DMN co-activation during rest, and higher cognitive status measured by MMSE score. This relationship was localized to the posterior cingulate and precuneus, and was greater in extent with GM correction, indicating it is not an artifact of atrophy, but rather that structural differences tended to hide the relationship. This result suggests that those patients demonstrating a healthier pattern of increased resting-state DMN integration show comparably better MMSE scores, despite no appreciable change between states in the group as a whole. This may reflect a more functionally intact DMN system that is still able to upregulate integration within these key nodes. Indeed, the areas of precuneus and posterior cingulate showing this relationship overlapped appreciably with regions showing significant resting state increases in the healthy controls alone. Critically, this relationship to cognitive status was unique to this measure of DMN modulation. Static measures of the DMN during rest or task alone exhibited no significant relationship to cognitive status in AD patients. Multiple recent studies have also failed to find significant associations between resting DMN integrity and cognitive status in mild AD, despite showing group differences (Zhou et al. 2010; Agosta et al. forthcoming; Binnewijzend et al. forthcoming). Taken together, our results suggest that a simple resting-state acquisition may be suitable for detecting group level deficiencies in AD patients, but show a poor ability to predict individual

![Figure 7. Voxel-wise regression of DMN modulation and MMSE score in patient group.](http://cercor.oxfordjournals.org/doi/abs/10.1093/cercor/bht096)
cognitive status. The present findings suggest that a dynamic measurement of DMN modulation may provide a more clinically useful indicator of a patient’s status than a single task or resting-state acquisition alone.

**Methodological Issues**

The resting-state acquisition was collected following the task, and so we cannot rule out the possibility that abnormalities noted at rest may reflect alterations occurring during the task runs. Our attempt to equalize the success between the groups should minimize this concern. For patient comfort, we collected only a single resting run, and the task data were acquired first to keep it close in time to the pre-scan practice. Future work to examine scan order effects using a pre- and post-task resting scan could address this issue.

The task acquisition included both task blocks and fixation periods, as opposed to continuous performance tasks used in some previous work (Fransson 2006; Calhoun et al. 2008; Fransson and Marrelec 2008). This was done to ensure patients and controls were able to keep up with the task demands over the course of the run, and to allow traditional univariate analyses of task data, results of which will be reported separately. It is possible that this structured task-fixation cycle could alter sensitivity to group differences due to the short periods of peak DMN activity during fixation blocks. However, the measure of DMN co-activation relies on identifying voxels that show both increases and decreases in activation akin to the overall group component, rather than on subtraction analysis comparing magnitude of activation between tasks, and even when both runs of task were used, no significant group differences were seen. Additionally, passive rest is also associated with significant fluctuations in activation magnitude within the DMN, rather than demonstrating tonic high activity (see Supplementary Fig. 1; see also Harrison et al. 2008), though there is no consensus as to a normal temporal pattern of DMN activity during unstructured rest. Finally, comparisons of task to rest suggest that the DMN was largely similar between states in AD patients, and showed restricted areas of greater co-activation in controls, suggesting that there was not a wholesale difference in DMN co-activation between these states. It may be challenging to develop a continuous performance task that is both engaging and simple enough for AD patients to perform successfully. Nevertheless, future work using continuous performance tasks is an important means of replicating and extending the present findings.

**Conclusion**

To our knowledge this is the first study to examine DMN abnormalities and modulation across different cognitive states in patients with AD. We found evidence for resting-state dysfunction in regions that are in line with the existing literature. In the task setting, however, patients and controls showed indistinguishable DMN patterns. This striking discrepancy across states was explained by a relative increase of DMN co-activation in healthy controls during rest, largely within areas overlapping a proposed MTL subsystem of the DMN. MMSE scores in patients were uniquely predicted by the degree of DMN modulation. These results have 3 key implications: First, they suggest that resting-state scans may be more sensitive to DMN abnormalities in AD when compared with a simple task that patients perform well. This supports the continued use of resting-state fMRI for detection and tracking of DMN dysfunction in AD. Secondly, this study demonstrates for the first time salient modulation of the DMN in healthy older adults, and an apparent loss of this capacity in mild AD. Finally, a measure of DMN modulation may be a better predictor of cognitive status in early disease than a static measurement during rest or task. These results argue against treating DMN dysfunction as a fixed, invariant feature of AD. Studies in earlier stage disease (i.e. amnestic MCI) and in pre-symptomatic at-risk populations could prove useful in determining the trajectory of disrupted DMN modulation, and investigate its relationship to future decline or treatment response.

**Supplementary Material**

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

**Funding**

This project is fully funded by the Canadian Institutes of Health Research (MOPT106485 and MT13129). Mr. Schwindt is supported by a Vanier Canadian Graduate Scholarship from CIHR and MD/PhD award from the McLaughlin Centre for Molecular Medicine at the University of Toronto. Dr. Masellis is funded by the Department of Medicine, Sunnybrook Health Sciences Centre and a CIHR Clinician Scientist Award. Dr. Grady is supported by a Canada Research Chair in Neurocognitive aging and CIHR. Dr. Black is supported by the Department of Medicine and the Brill Chair in Neurology at the University of Toronto and Sunnybrook Health Sciences Centre, The Sunnybrook Research Institute, and the Heart and Stroke Foundation Centre for Stroke Recovery.

**Notes**

We thank Rafal Janik for technical assistance, Gregory Szilagyi for development of stimulus presentation software, and the patients and families who participate in our research. **Conflict of Interest:** None declared.

**References**


Binneuwijzend MAA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, Adriaanse SM, Damoiseaux JS,


