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Neuroimage. Author manuscript; available in PMC 2009 February 1.

Published in final edited form as:
Neuroimage. 2008 February 1; 39(3): 1324–1332. doi:10.1016/j.neuroimage.2007.09.064.

Neuro-imaging of individuals with Down syndrome at-risk for dementia: evidence for possible compensatory events

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Abstract

Background—We report functional and structural brain indicators that may precede the onset of dementia in individuals with Down syndrome (DS).

Methods—Middle-aged adults with DS (N=19), a group known to be at high risk for dementia, were studied with (1) positron emission tomography (PET) to determine cerebral glucose metabolic rate (GMR), (2) structural magnetic resonance imaging (MRI) to determine gray matter volume (GM), and (3) ratings of potential dementia indicators based on a structured interview of caregiver observations designed to evaluate individuals with low intelligence.

Results—Although none of the participants showed clinical signs of dementia, ratings of dementia indicators were correlated to both functional and structural imaging. The strongest correlations ($p<.05$, corrected for multiple comparisons) included the combination of *higher* GMR and decreased GM volume in parts of the temporal cortex, including the parahippocampus/hippocampus, in the thalamus, caudate, and frontal lobe (BA 47).

Interpretation—The combination of *increased* GMR overlapping with *less* gray matter in these areas may be consistent with a compensatory brain response to an early stage of the disease process.

Keywords

Down syndrome; Alzheimer's disease; dementia; pre-clinical AD; MRI; PET; voxel-based morphometry; brain imaging

Early neuropathological signs of Alzheimer's disease (AD) are evident predominantly in the temporal/entorhinal cortex (Braak and Braak 1997). Brain imaging studies in AD generally support this view by showing decreased activity or gray matter tissue loss in these areas (Jagust, Haan et al. 1996; Herholz, Nordberg et al. 1999; de Leon, Convit et al. 2001; Silverman, Small

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et al. 2001; Alexander, Chen et al. 2002; Karas, Burton et al. 2003; Thompson, Hayashi et al. 2003; Karas, Scheltens et al. 2004; Mosconi, Perani et al. 2004; Mosconi, Pupi et al. 2004; Bokde, Teipel et al. 2005; Csernansky, Wang et al. 2005; Fleisher, Houston et al. 2005; Hirata Y Fau - Matsuda, Matsuda H Fau - Nemoto et al. 2005; Mosconi 2005; Mosconi, Tsui et al. 2005; Mungas, Harvey et al. 2005; Reiman, Chen et al. 2005; Salmon, Lespagnard et al. 2005; den Heijer, Geerlings et al. 2006). The posterior cingulate also shows robust decreases in gray matter in early AD (Minoshima, Giordani et al. 1997; Minoshima, Cross et al. 1999). Since middle-aged people with Down syndrome (DS) are at increased risk for dementia thought to be of the Alzheimer's type (Wisniewski, Dalton et al. 1985; Oliver and Holland 1986; Lott and Head 2001), structural or metabolic brain changes in DS, especially in the temporal lobes and/or posterior cingulate, may predict the onset of dementia. There is some functional brain imaging evidence to support this view (Schapiro, Ball et al. 1988; Deb, de Silva et al. 1992; Haier, Chueh et al. 1995; Dani, Pietrini et al. 1996; Pietrini, Dani et al. 1997). However, these studies showed inconsistent results, often based on small sample sizes (and often without normal controls), and relied on early PET imaging techniques lacking cognitive activation and/or precise anatomical localization of findings. Similarly, recent structural imaging studies in DS show several areas where GM loss is related to dementia, pre-clinical AD, or aging (Raz, Torres et al. 1995; Pearlson, Breiter et al. 1998; Aylward, Li et al. 1999; Prasher V Fau - Cumella, Cumella S Fau - Natarajan et al. 2003; Teipel, Alexander et al. 2004; Hirata, Matsuda et al. 2005; Teipel, Pruessner et al. 2006; Teipel and Hampel 2006), although there are inconsistencies among these studies and only one includes prospective data (Aylward, Li et al. 1999).

The DS model of Alzheimer's disease is useful for research because middle aged individuals can be identified prior to any clinical signs of dementia and studied longitudinally with an increased probability of conversion. The actual rate of conversion varies among studies, but the most recent data on 506 individuals with DS (ages 45–77) show the highest prevalence of dementia is 32.1% in the age group 55–59; the rate is 17.7% in 50–54 year olds and 8.9% in 45–49 year olds (Coppus, Evenhuis et al. 2006). We conducted a prospective study using PET and MRI starting with middle-aged persons with DS, none of whom showed clinical signs of dementia when they entered the study. Previously, we reported the baseline MRI data, comparing the DS group to matched normal controls using voxel-based morphometry (VBM) to determine regional gray and white matter volumes. The DS group showed less gray matter (GM) in several areas throughout the brain, including cerebellum, anterior cingulate, frontal lobe and temporal lobe, including part of the hippocampus. They also showed increased GM compared to the controls in the parahippocampal gyrus and in the inferior brainstem (White, Alkire et al. 2003). We also have reported baseline PET results comparing four groups: the same middle-aged, non-demented Down syndrome group; the same middle-aged normal controls; patients with Alzheimer's disease; and matched control seniors. Results showed *increased*glucose metabolic rate (GMR) in areas of the temporal lobes in the DS group in the exact same areas where AD showed decreased GMR, compared to respective control groups (Haier, Alkire et al. 2003). There were also areas where, compared to their respective controls, both the AD and the DS groups showed lower GMR. These areas included the posterior cingulate and the fusiform gyrus.

Our early reports, however, did not address which, if any, of these structural and functional findings might predict dementia and which might be due to the characteristics of DS itself. In this report, therefore, we examine whether the PET and/or MRI findings predict early indications of dementia in the DS subjects. Only one DS case converted to clinically diagnosable dementia using DSM IV criteria during the 4 year follow-up to date, so here we use a behaviorally-based rating to assess early indicators of dementia which may precede a clinical diagnosis. Based on our 2003 report, we hypothesized that region-specific GMR increases may be the result of a compensatory response which makes the brain work harder in

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the very earliest stages of the dementing process as GM loss begins (Head, Lott et al. 2007). Therefore, in this report we first test whether either increased GMR or decreased GM, at baseline before any clinical diagnosis of dementia, correlates to ratings of early indicators of dementia. Second, we test whether any brain areas show the combination of increased GMR and decreased GM and, if so, whether this combination correlates to the ratings of dementia indicators.

Materials and methods

Subjects

We screened over 40 people with DS between the ages of 34 and 55 to cover the range of middle age risk. These people were identified from the University clinic and from local group homes, eliminating cases where IQ was less than 45, cases with severe physical disabilities or seizures, or medical illnesses, cases where there was any clinical evidence of dementia, and cases whose guardians would not consent to the required imaging. A total of 21 individuals with DS were entered into the study and 19 of those completed useable PET and MRI scans as well as cognitive evaluations. None met clinical DSMIV criteria for Alzheimer's disease. These 19 cases included 10 men and 9 women (age range was 34–52, mean= 41.8, sd= 6.3; WAIS-III FSIQ range 47–72, mean=55.7, sd=6.8); most completed karyotyping. Eighteen of these 19 were included in our previous MRI report (White, Alkire et al. 2003) and 17 of these 19 were included in our previous PET report (Haier, Alkire et al. 2003). All subjects and/or their care-givers/guardians gave informed consent in accord with procedures required and approved by the University Institutional Review Board.

Assessing early indicators of dementia

The diagnosis of dementia in people with DS is exceedingly difficult because clinical and behavioral measures like the Mini Mental Status Examination (MMSE) are confounded by low intelligence (Aylward, Burt et al. 1997; Deb and Braganza 1999). For this study where a main goal is to identify brain changes associated with the earliest indicators of dementia, before a clinical diagnosis is possible, we had an even more difficult problem. The Dementia Questionnaire for Mentally Retarded Persons (DMR)(Evenhuis 1992; Evenhuis 1996) was developed to help make a diagnosis of dementia, especially when based on changes in DMR scores over time, corrected for IQ. Here, we used the DMR assessed at baseline to determine the presence of cognitive and behavioral signs of possible dementia. No one item or set of items assessed by the DMR are sufficient to indicate dementia, but we used the total number of items present as an index of possible pre-clinical AD. Every subject entered the study at a different, unknown stage of pre-clinical AD (from only a few years away from a diagnosis to never getting a diagnosis), so the total DMR score was judged to be a reasonable quantitative index for correlating to neuroimaging data.

Two subsequent studies provide some support for using the DMR in this way. One study (Shultz, Aman et al. 2004) used the DMR and similar measures to differentiate between demented (n=19) and non-demented (n=19) adults with mental retardation, including Down syndrome. Dementia was determined by clinical interview and DSM-IV or ICD-10 criteria. They found the DMR scales assessed at one point in time showed the strongest differentiation between groups ($p<.001$). For the demented group, the mean for the sum of cognitive scores was 26.7 (sd=7.2) and it was 11.0 (sd=10.7) for the non-demented group; for the sum of social scores the mean was 24.5 (sd=11.2) for the demented group and 7.4 (sd=6.1) for the non-demented group. The magnitude of the group mean differences suggests that total scores can be an index of degree of impairment. The second study determined dementia status in 273 mentally retarded adults including 186 with DS (Silverman, Schupf et al. 2004). They also showed that DMR scores at a single point in time could distinguish demented from non-

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demented groups, even when dementia status was “questionable” or “possible“ (see their table 3). However, many of the questionable and possible cases of dementia scored below the DMR cut-off criteria, suggesting that a cutoff score was not the best way to classify dementia versus non-dementia. Compared to the single time point score, DMR change scores over an 18-month follow-up period did not improve classification substantially. The results from both these studies suggest that it is reasonable to use total DMR scores at a single point in time as an index of degree of dementia.

We are unaware of a better way to quantify individual differences in the earliest potential indicators of future dementia for a research purpose, especially in a low intelligence group. We emphasize that our use of the DMR does not diagnose dementia, but rather it serves as an index of possible future dementia. Correlations between this index and brain changes in areas known to be related to AD would support this view, as shown in the results below.

The DMR is an informant-based measure of 50 items covering 8 areas of cognitive and emotional functioning. These include: short-term memory (7 items), long-term memory (8 items), spatial and temporal orientation (7 items), speech (4 items), practical skills (8 items), mood (6 items), activity and interest (6 items), and behavioral disturbance (6 items). Responses to each item are limited to, “normally yes”, “sometimes” or “normally no” (ratings of 2, 1, 0, respectively). The ratings are summarized as the sum of cognitive (first three subtests) and the sum of social scores (last five subtests) with higher scores indicating more indicators of impairment. For all analyses, we used the DMR total score (rank ordered) which is based on the sum of all 8 subscales (N=19, mean/sd = 13.0/5.6; range 0 to 35). Since the total scores were not normally distributed, we used their rank order to compute all correlations with neuroimaging data. Since each subject had a different care-giver, there was no opportunity to assess inter-rater reliability in this sample, although inter-rater reliabilities for each subscale are reported to be .68 to .94 for 7 subscales and .44 for one subscale (behavioral disturbance) (Evenhuis 1992).

In this sample, DMR scores correlated .50 ($p < .025$, 1 tailed) with FSIQ; MMSE scores correlated .88 ($p < .005$, 1 tailed) with FSIQ. It should be noted that all but two of the 19 DS subjects had FSIQ scores between 47 and 65; the highest FSIQ’s were 68 and 72. FSIQ was also correlated to total GM volume, $r = .65$ ($p < .005$). Therefore, we used total brain volume as a nuisance variable in the SPM analyses of neuroimaging/DMR relationships described below and we also added FSIQ as a nuisance variable in supplemental analyses to assess any independent influence it might have on results.

Imaging

As described previously(Haier, Alkire et al. 2003), each subject completed glucose metabolic rate (GMR) determinations using PET with [^{18}F]flurodeoxyglucose (FDG) as the metabolic tracer while performing a cognitive task, the Continuous Performance Test (CPT) of attention. Earlier PET work comparing young and old, non-demented DS adults showed GMR differences only during an activation condition and not during a rest (no-task) condition (Pietrini, Dani et al. 1997), and the CPT was used in our previous PET study of DS (Haier, Chueh et al. 1995). This test required the subject to watch single digits in random order flash on a screen with the instruction to press a button each time a zero appeared (20%). CPT performance was calculated as d’ (probability corrected true hit rate minus false hit rate). The CPT was performed for 32 minutes following the injection of 5 mCi of FDG. Following this uptake period, emission scans were obtained with a GE2048 PET scanner (FWHM resolution 4.5mm in plane). Images were corrected for attenuation based a transmission scan completed before FDG injection. Each subject also completed a structural MRI. We used a1.5-T clinical Phillips Eclipse scanner (T1-weighted, volumetric SPGR; FOV 24 cm; flip angle 40 degrees; TR 24; TE 5; 120 contiguous 1.2-mm-thick axial slices in 256×256 matrix).

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Data analyses

Our overall analysis strategy was straightforward. We began by determining the brain areas where PET GMR data correlated to DMR scores. We then determined the brain areas where MRI GM data correlated to DMR scores. Finally, we determined the brain areas where there were both GMR and GM correlations with DMR scores.

All PET and MRI images were normalized, and smoothed to 12mm using Statistical Parametric Mapping (SPM2; The Wellcome Department of Imaging Neuroscience, University College London). For PET pre-processing and normalization, a standard SPM2 template was used. PET analyses were based on proportional scaling; thus, all PET values used in analyses are relative, not absolute. For MRI, study specific templates were created from all DS and matched control subjects as described previously (White, Alkire et al. 2003). MRIs were analyzed using optimized voxel-based morphometry (VBM) to determine gray matter volumes as in previous studies (Ashburner and Friston 2000; Ashburner and Friston 2001; Good, Johnsrude et al. 2001; Good, Scahill et al. 2002; White, Alkire et al. 2003).

We used SPM2 to identify the PET and the MRI areas which correlated to DMR ratings. For the MRI analyses, total brain GM was entered as a nuisance variable in the SPM design matrix to partial out any variance it might contribute to the findings. For analyses of PET data alone, we included age, sex, and CPT performance (d') as a nuisance variable because any task used during functional imaging in subjects with varying degrees of impairment will produce individual differences which could confound brain function patterns. We also repeated these analyses adding FSIQ as a nuisance variable to determine if it influenced results, although FSIQ had a restricted range and was correlated with total GM (r= .65). To determine the overlap between any areas where baseline PET and MRI both correlated to baseline DMR score rank, we used the xjView SPM extension (Cui & Li, Human Neuroimaging Lab, Baylor College of Medicine) and used the threshold of $p<.028$ for GMR and for GM analyses separately to produce a combined p level of <.0008 (i.e. .028×.028) for identifying overlapping voxels between the two analyses. All SPM2results were converted from standard MNI (Montreal Neurological Institute) coordinates to coordinates used in the Talairach and Tournoux Atlas (Talairach and Tournoux 1988) using the SPM MNI2TAL utility; our tables show coordinates for the maximum voxel value for the cluster. PET and MRI results are displayed on the single subject T1 template in SPM (Colin), skull stripped and spatially normalized to the standard SPM PET template.

Our sample size is relatively large for imaging studies of DS, but relatively small for dealing with the myriad of analyses and voxel-based comparisons inherent in neuroimaging studies. Without more subjects and more statistical power, type I errors can not be ruled out. Although we document all correlation findings at $p<.001$ for comparison to earlier studies and for future hypothesis generation, we limit our discussion to the more statistically conservative findings at $p<.05$, corrected for multiple comparisons to minimize type II errors. Note that whenever we use the terms "increased" or "decreased" GMR or GM, we are referring to relative relationships within this group of subjects since SPM2 normalizes each subject's data to the full sample.

Results

Correlating DMR scores separately to GMR and to GM

To test the hypothesis that increased GMR or decreased GM precedes the onset of dementia, we correlated the DMR total score to GMR and to GM volume. All analyses are based on using the rank order of DMR scores (using raw scores produced substantially the same results for all analyses). At $p<0.001$, higher DMR scores (i.e. more indications of impairment) were

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associated with higher GMR in a number of areas throughout the brain. These included the pons, areas in the temporal lobes (BAs 38, 20, 39), the lentiform nucleus (including the globus pallidus and caudate), and the parahippocampus. Higher DMR scores also were associated with less GM ($p<0.001$) in the thalamus, the parahippocampal gyrus, and the temporal lobes (BAs 42, 37). The anatomical locations of these results for both increased GMR and for decreased GM are detailed in Table 1 and shown in Figure 1 ($p<.001$). Interestingly, there were no significant correlations between decreased GMR in any areas and DMR ratings ($p<.001$). At $p<.001$, increased GM was correlated to higher DMR in only one small part of the right parietal lobe (411 voxels, T=4.41, co-ordinates 17, −37, 65, not shown). All these analyses were repeated adding FSIQ as a nuisance variable to determine any influence of intelligence on the results. None of the significant results changed appreciably. Excluding CPT performance as a nuisance variable from the PET analyses also had no appreciable effect.

Brain areas where the combination of *both* GMR *and* GM correlate to DMR ratings

The compensatory hypothesis may be most strongly represented in areas that show both increased GMR and decreased GM (although increased GMR may be associated with compensation without a decrease in GM or even with an increase in GM). We next tested whether any areas showed both increased GMR correlated to DMR score and decreased GM correlated to DMR score. This overlap was determined using xjView in SMP2 (combined PET/MRI voxel X voxel $p<.0008$) on the results obtained above. Table 2 details the location of these brain areas. Figure 2 (left panels) shows the most significant areas of overlap ($p<.05$, corrected for multiple comparisons). They are in the parahippocampus/hippocampus gyrus, the middle temporal gyrus, thalamus, caudate, cerebellum, and BA 47 in the frontal lobe. Figure 3 shows scatterplots for both GMR (positive) and GM (negative) correlations with DMR scores at the site of the strongest area of overlap in the parahippocampus. As shown in the scatterplots, these correlations are not due to outliers, nor are any of the other correlations shown in Figures 1 and 2.

Since increased GMR may also be associated with increased GM, we used the same xjview analysis to identify any areas with this combination ($p<.0008$). These areas are detailed in Table 3 and include the pons, inferior and superior temporal lobe, part of BA 47, the lentiform nucleus, and the parahippocampus. The most significant areas (pons and BA 20; $p<.05$, corrected) are shown in Figure 2 (right panels). None of these specific voxel clusters overlap with the ones identified in the left panels of Figure 2. At $p<.0008$, no areas were found where DMR correlated to either the combination of low GMR/low GM or to the combination of low GMR/high GM.

Discussion

These results add to the growing evidence that neuroimaging can identify early brain signs of dementia before clinical symptoms are apparent. For the combination of increased GMR (i.e. higher GMR values are correlated to higher DMR scores) and decreased GM (i.e. lower GM values are correlated to higher DMR scores), these findings are in the parahippocampus/hippocampus, the caudate, thalamus and BA 47, as shown in Figure 2 (left panels). For the areas with the combination of both increased GMR and increased GM, shown in Figure 2 (right panels), the findings are in the pons and part of the inferior temporal gyrus near BA 20.

Finding DMR correlations with the combination of increased GMR and decreased GM co-existing in the same areas is consistent with an interpretation of increased metabolism as a compensatory response to gray matter loss (Haier, Alkire et al. 2003; Head, Lott et al. 2007). There is supporting evidence of compensation from our previous neuropathology study of middle-aged DS individuals with dementia who show neuronal sprouting in temporal lobe areas (Head, Lott et al. 2003), from a study showing synaptic hypertrophy (Dekosky and Scheff 1990), and from a study of mild cognitive impairment (MCI) showing up-regulation of choline

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acetyltransferase activity in the hippocampus and in the frontal lobe (DeKosky, Ikonomovic et al. 2002). Some imaging studies also have reported evidence of increased regional brain activity, especially in temporal or frontal lobe areas, in early AD dementia, in MCI, and in normal individuals at genetic risk for AD, findings consistent with a compensatory hypothesis (Grady, Haxby et al. 1993; Bookheimer, Strojwas et al. 2000; Grady, McIntosh et al. 2003; Dickerson, Salat et al. 2004; Bondi, Houston et al. 2005; Dickerson, Salat et al. 2005).

Our finding that DMR correlates with GMR and GM overlap in BA 47 is also consistent with frontal-subcortical models of dementia (Garraux, Salmon et al. 1999; Tekin and Cummings 2002). The observation of DMR correlating to increased GMR and to decreased GM in the caudate and lentiform nucleus may be consistent with evidence suggesting a role of the dopaminergic system in AD (Perez, Lazarov et al. 2005) and with a possible dysfunction or disconnection between parts of the basal ganglia and the frontal lobe in DS (Haier, Hazen et al. 1998). Our thalamus finding may be part of this network, but these areas are not often reported in similar studies of dementia. Whether these areas are unique to pre-clinical AD in DS or represent a very early stage of AD in general can not yet be determined, although there is some VBM evidence of caudate and thalamus atrophy in AD (Karas, Burton et al. 2003). Increased regional GMR is also consistent with earlier PET studies showing higher GMR related to poor or inefficient performance of complex cognitive tasks (Haier, Siegel et al. 1988; Haier, Siegel et al. 1992; Haier 1993; Haier, Chueh et al. 1995).

The areas showing decreased GMR in this group of DS relative to matched controls and to AD subjects that we observed in our previous report (Haier, Alkire et al. 2003), do not correlate to dementia ratings in this sample. A small part of the posterior cingulate (linked to early AD (Minoshima, Giordani et al. 1997; Minoshima, Cross et al. 1999)) may be an exception (see table 3). One possibility for not finding strong correlations between the DMR and decreased GMR is that the dementia which develops in DS may not be exactly the same in origin or in sequence of progression as that which develops in AD, and there even may be more than a single sequence in AD(Shiino, Watanabe et al. 2006). Individuals with DS over-express multiple genes that may modify or accelerate AD progression. Any such effects, however, may not be apparent in neuropathology studies of adults with clinical dementia, which typically come to study as end-stage cases.

All functional imaging studies can only be interpreted in the context of the specific task performed by subjects. In this case, we chose a simple test of attention, the CPT, for the PET FDG uptake period. Other tasks could well have identified other brain areas; there is no consensus on a standard task for functional imaging studies which would maximize activation differences in areas vulnerable to dementia. This limitation, however, does not apply to structural imaging. We believe the combination of the two provides more compelling data than either method alone.

The most difficult problem facing every prospective study of people at risk for dementia is that, invariably, the subjects all are at a different stage of any pre-clinical disease processes when they enter the study and there is no way to determine this staging at present. Evaluating pre-clinical AD with a battery of measures may prove more sensitive than the DMR alone. Imaging individuals with new compounds to label amyloid deposits also shows considerable promise for this(Shoghi-Jadid, Small et al. 2002; Klunk, Engler et al. 2003).

Data from this and other neuroimaging studies indicate that both increases and decreases in brain activity precede clinical dementia depending on when in the disease process imaging occurs. These characteristics change over time in different ways in different brain areas as GM loss progresses. Therefore, any one of several neuroimaging results for an individual may be predictive of subsequent dementia depending on when in the pre-clinical disease process

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scanning occurs. For example, even before brain imaging detects decreased function or tissue loss in temporal lobes, it may be possible to identify relative increases in function and decreases in tissue in other areas which may define a group of people at risk for dementia and who may benefit from future prophylactic treatments. Also, understanding whether increased function in combination with decreased tissue reflects a compensatory mechanism may be particularly important if such a mechanism can be prolonged, enhanced or stimulated by novel agents (Head, Lott et al. 2007). If such research shows promise, lower cost imaging techniques may be developed to make screening more practical. The large scale NIH Alzheimer's Disease Neuroimaging Study, now underway, may provide data to replicate our observations and to test the predictive validity of regionally increased GMR (or other signs of increased activity such as measured by fMRI), especially in combination with GM loss, as indicators of future dementia.

Acknowledgement

This project was supported by grant RO1 HD-37427 (R. Haier, PI) from NICHD and, in part, by AG21912 (I. Lott, PI), P50-AG 16593 (C. Cotman, PI), and the "My Brother Joey Neuroscience Fund" (I. Lott, PI).

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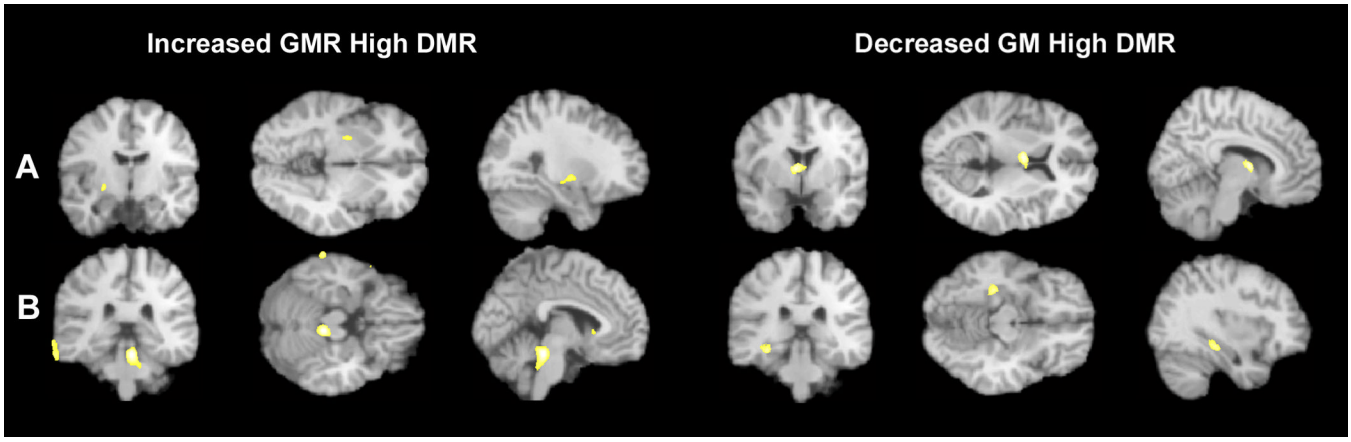

Figure 1.
Correlations between increased glucose metabolic rate (GMR) assessed with PET and higher dementia ratings (left panels) and, correlations between decreased gray matter (GM) assessed with VBM and higher dementia ratings (right panels); all correlations ($p<.001$). Names and anatomical locations for these areas are shown in table 1.

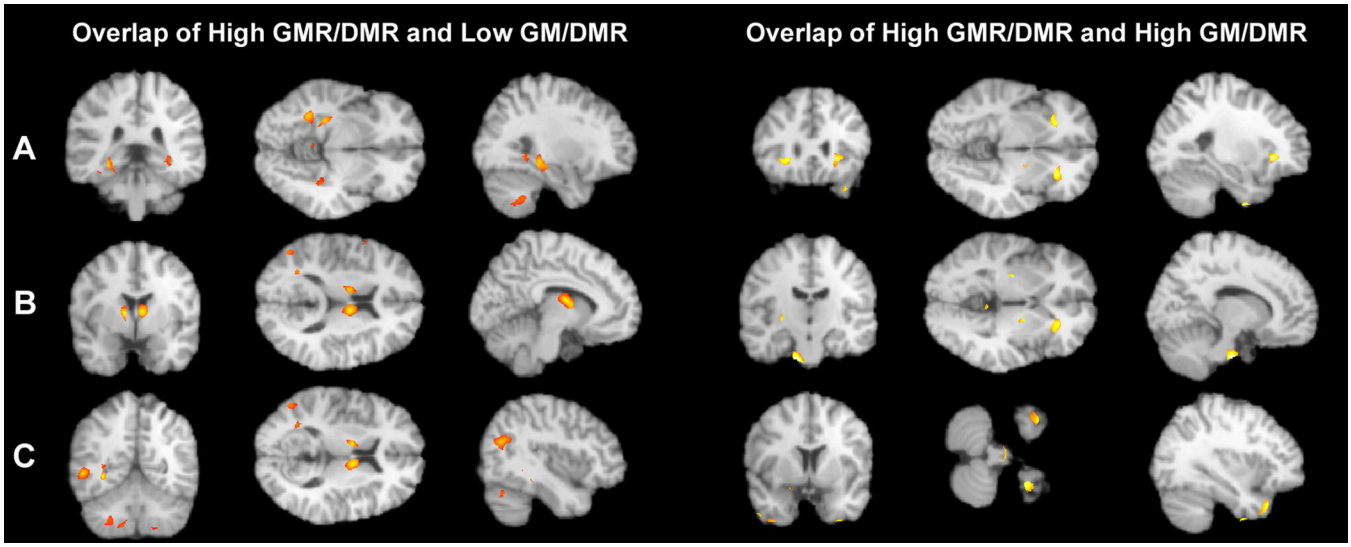

Figure 2.
LEFT: Areas where both increased PET glucose metabolic rate and decreased VBM gray matter correlate to higher dementia ratings ($p<.05$, corrected). Row A shows the parahippocampus/hippocampus, row B shows the caudate, row C shows middle temporal gyrus. RIGHT: Areas where both increased PET glucose metabolic rate and increased VBM gray matter correlate to higher dementia ratings.. Row A shows BA 47 ($p<.001$); row B shows the pons and row C shows the inferior temporal gyrus, BA 20 ($p<.05$, corrected). Names and anatomical locations for all overlapping areas are shown in tables 2 and 3.

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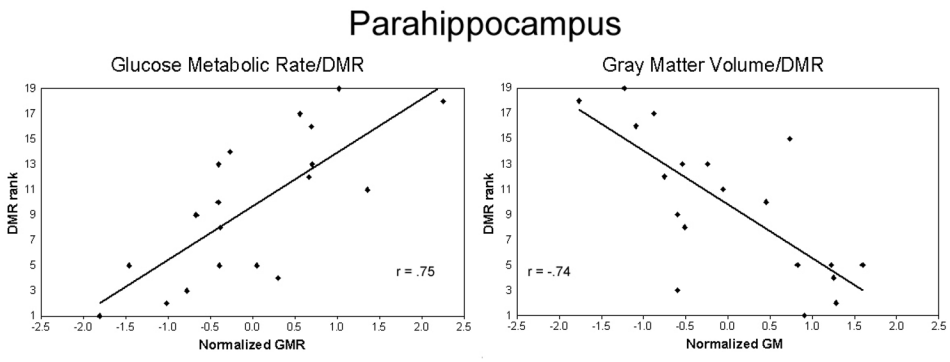

Figure 3.

Scatterplots show the correlations between of DMR total score (rank) with GMR (left) and GM (right). GMR and GM normalized values are taken from the maximum voxel within the parahippocampal cluster shown in table 2 (co-ordinates −34, −50, 1) representing the area with the strongest overlap of GMR (positive) and GM (negative) correlations with DMR ratings.

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Table 1

Brain areas * where either increased GMR or decreased GM correlates to higher DMR scores at baseline (p<.001)

Increased GMR Cluster size	t	z	x	y	z	
2430	5.12	3.78	9	−35	−17	Right Pons
780	4.56	3.51	−57	12	−26	Left Superior Temporal Gyrus BA 38
633	4.34	3.40	−70	−36	−17	Left Middle Temporal Gyrus
	4.12	3.28	−72	−35	−7	Left Middle Temporal Gyrus BA 21
447	4.29	3.37	−53	−19	−36	Left Inferior Temporal Gyrus BA 20
314	4.11	3.28	−35	−68	25	Left Middle Temporal Gyrus BA 39
260	4.11	3.27	−24	−10	−3	Left Lentiform Nucleus Lateral Globus Pallidus
	3.84	3.12	−23	−20	−7	Left Limbic Lobe BA 28
87	4.04	3.24	−14	3	4	Left Lentiform Nucleus Lateral Globus Pallidus
123	4.03	3.23	−45	24	−31	Left Superior Temporal Gyrus A 38
147	4.02	3.23	−30	−20	−39	Left Inferior Temporal Gyrus BA 20
82	3.98	3.20	8	18	−1	Right Caudate Head
40	3.89	3.15	19	8	−40	Right Limbic Lobe Uncus BA 38
18	3.86	3.13	−33	−53	1	Left Limbic Lobe Parahippocampal Gyrus BA 19
Decreased GM						
1116	4.88	3.76	−3	−1	9	Left Thalamus Anterior Nucleus
	3.82	3.17	6	1	5	Right Caudate Caudate Head
1276	4.63	3.63	−38	−46	0	Left Limbic Lobe Parahippocampal Gyrus BA 19
	4.33	3.47	−32	−33	−10	Left Limbic Lobe Parahippocampal Gyrus BA 36
	4.17	3.38	−39	−36	−6	Left Temporal Lobe Fusiform Gyrus BA 37
38	3.95	3.25	64	−13	11	Right Temporal Lobe Transverse Temporal Gyrus BA 42
35	3.89	3.21	−53	−59	5	Left Middle Temporal Gyrus BA 37

* All Brodmann area (BA) locations are best estimates from Talairach Atlas co-ordinates (x, y, z) of maximum voxel value.

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Table 2

Brain areas where combination of both increased GMR and decreased GM correlate to higher DMR score (p< .028X.028=.0008)

Cluster size	t	z	x	y	z	
1501	14.98	6.50	−34	−50	1	Left Limbic Lobe Parahippocampal Gyrus BA 19*
	7.27	4.76	−30	−60	17	Left Middle Temporal Gyrus BA 19
	5.67	4.14	−31	−57	10	Left Middle Temporal Gyrus BA 19
2589	10.26	5.62	−52	−60	4	Left Middle Temporal Gyrus BA 37*
	6.59	4.52	−52	−68	14	Left Middle Temporal Gyrus BA 39
	6.13	4.34	−53	−73	6	Left Middle Occipital Gyrus BA 19
1262	10.16	5.60	−36	−66	26	Left Middle Temporal Gyrus BA 39*
1136	10.05	5.57	−9	−1	8	Left Sub-lobar Thalamus*
1994	9.83	5.51	10	1	10	Right Sub-lobar Caudate Caudate Body*
1705	9.53	5.44	−28	−32	−6	Left Limbic Lobe Parahippocampal Gyrus Hippocampus*
	5.37	4.01	−13	−44	−15	Left Cerebellum Anterior Lobe
	5.31	3.97	−19	−39	−11	Left Limbic Lobe Parahippocampal Gyrus BA 36
988	9.15	5.34	−48	−65	−24	Left Cerebellum Posterior Lobe*
219	7.82	4.95	−32	35	1	Left Frontal Lobe Inferior Frontal Gyrus BA 47*
489	7.18	4.74	28	−47	−36	Right Cerebellum Posterior Lobe
382	7.09	4.70	40	−38	−1	Right Limbic Lobe Parahippocampal Gyrus BA 19
	4.98	3.81	40	−35	−7	Right Limbic Lobe Parahippocampal Gyrus BA 36
311	6.67	4.55	−1	−44	−7	Left Cerebellum Anterior Lobe
	4.55	3.59	4	−54	−8	Right Cerebellum Anterior Lobe
708	6.15	4.34	40	−76	−25	Right Cerebellum Posterior Lobe
	5.72	4.16	47	−68	−26	Right Cerebellum Posterior Lobe
1013	6.09	4.32	−25	−52	−38	Left Cerebellum Posterior Lobe
13	5.99	4.28	−31	−95	24	Left Middle Occipital Gyrus BA 19
356	5.69	4.15	−10	−57	−46	Left Cerebellum Posterior Lobe
52	5.55	4.08	−37	−38	−12	Left Temporal Lobe Fusiform Gyrus BA 37
61	5.53	4.08	−61	12	14	Left Inferior Frontal Gyrus BA 44
255	5.06	3.86	20	−62	−49	Right Cerebellum
16	4.69	3.67	−35	−85	27	Left Superior Occipital Gyrus BA 19

* p<.05 corrected for multiple comparisons; all Brodmann area (BA) locations are best estimates from Talairach Atlas co-ordinates (x, y, z) of maximum voxel value.

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Table 3

Brain areas where combination of both increased GMR and increased GM correlate to higher DMR score (p< .028×.028=.0008)

Cluster size	t	z	x	y	z	
4081	9.76	5.28	−9	−18	−36	Left Brainstem Pons*
	8.17	4.88	−57	−37	−27	Left Temporal Lobe Fusiform Gyrus BA 20
	7.79	4.77	−18	−27	−31	Left Brainstem Pons
352	8.68	5.02	34	−2	−47	Right Inferior Temporal Gyrus BA 20*
969	8.23	4.89	30	32	−3	Right Inferior Frontal Gyrus BA 47
142	8.01	4.83	−23	−13	−3	Left Lentiform Nucleus Lateral Globus Pallidus
473	7.58	4.70	−25	26	−7	Left Inferior Frontal Gyrus BA 47
1108	7.40	4.65	−46	−8	−15	Left Inferior Temporal Gyrus BA 20
604	7.22	4.59	14	−59	−24	Right Cerebellum Anterior Lobe
768	7.17	4.58	41	24	−35	Right Superior Temporal Gyrus BA 38
	6.73	4.43	47	18	−36	Right Superior Temporal Gyrus BA 38
141	6.70	4.42	23	−3	−1	Right Lentiform Nucleus Putamen
273	6.63	4.39	8	−42	4	Right Limbic Lobe Parahippocampal Gyrus BA 30
	5.36	3.89	1	−38	11	Right Limbic Lobe Posterior Cingulate
538	6.28	4.26	−36	9	−45	Left Superior Temporal Gyrus BA 38
	5.97	4.14	−53	2	−39	Left Middle Temporal Gyrus BA 21
	5.47	3.94	−37	2	−47	Left Inferior Temporal Gyrus BA 20
929	6.00	4.15	−17	−73	−26	Left Cerebellum Posterior Lobe
	5.40	3.91	−26	−68	−27	Left Cerebellum Posterior Lobe Pyramis
14	5.06	3.75	−15	3	−15	Left Frontal Lobe Subcallosal Gyrus BA 34
13	4.46	3.46	56	−30	−25	Right Inferior Temporal Gyrus BA 20

* p<.05 corrected for multiple comparisons; All Brodmann area (BA) locations are best estimates from Talairach Atlas co-ordinates (x, y, z) of maximum voxel value.