

Altered functional connectivity in asymptomatic *MAPT* subjects

A comparison to bvFTD

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ABSTRACT

Objective: To determine whether functional connectivity is altered in subjects with mutations in the microtubule associated protein tau (*MAPT*) gene who were asymptomatic but were destined to develop dementia, and to compare these findings to those in subjects with behavioral variant frontotemporal dementia (bvFTD).

Methods: In this case-control study, we identified 8 asymptomatic subjects with mutations in *MAPT* and 8 controls who screened negative for mutations in *MAPT*. Twenty-one subjects with a clinical diagnosis of bvFTD were also identified and matched to 21 controls. All subjects had resting-state fMRI. In-phase functional connectivity was assessed between a precuneus seed in the default mode network (DMN) and a fronto-insular cortex seed in the salience network, and the rest of the brain. Atlas-based parcellation was used to assess functional connectivity and gray matter volume across specific regions of interest.

Results: The asymptomatic *MAPT* subjects and subjects with bvFTD showed altered functional connectivity in the DMN, with reduced in-phase connectivity in lateral temporal lobes and medial prefrontal cortex, compared to controls. Increased in-phase connectivity was also observed in both groups in the medial parietal lobe. Only the bvFTD group showed altered functional connectivity in the salience network, with reduced connectivity in the fronto-insular cortex and anterior cingulate. Gray matter loss was observed across temporal, frontal, and parietal regions in bvFTD, but not in the asymptomatic *MAPT* subjects.

Conclusions: Functional connectivity in the DMN is altered in *MAPT* subjects before the occurrence of both atrophy and clinical symptoms, suggesting that changes in functional connectivity are early features of the disease. *Neurology*® 2011;77:866-874

GLOSSARY

AD = Alzheimer disease; **BOLD** = blood oxygenation level-dependent; **bvFTD** = behavioral variant frontotemporal dementia; **DMN** = default mode network; **FOV** = field of view; **FTD** = frontotemporal dementia; **FWE** = familywise error; **ICA** = independent component analysis; **MPRAGE** = magnetization-prepared rapid acquisition gradient echo; **PPND** = pallido-ponto-nigral degeneration; **ROI** = region of interest; **TE** = echo time; **TIV** = total intracranial volume; **TR** = repetition time.

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder characterized by behavioral and language deficits.^{1,2} A large proportion of subjects with FTD have an autosomal dominant pattern of inheritance,^{3,4} with many showing mutations in the microtubule associated protein tau (*MAPT*) gene.⁵ Subjects with mutations in *MAPT* typically present with behavioral variant FTD (bvFTD), with poor semantic abilities,⁶⁻⁸ and show predominant temporal atrophy, with less severe involvement of frontal and parietal lobes.^{9,10} Families characterized by the presence of mutations in *MAPT* provide the ideal construct to identify preclinical disease changes. Case studies assessing imaging in asymptomatic *MAPT* carriers show

Supplemental data at
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Supplemental Data



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Table	Subject demographics ^a					
	MAPT controls (n = 8)	Asymptomatic MAPT (n = 8)	p Value	bvFTD controls (n = 21)	bvFTD (n = 21)	p Value
Female, n (%)	6 (75)	5 (62)	0.65	6 (29)	7 (33)	0.75
Age at MRI, y	49 (29 to 59)	39 (23 to 46)	0.16	64 (45 to 79)	58 (45 to 79)	0.05
Time from onset to MRI, y	NA	-2 (-19 to 5) ^b	NA	NA	5 (0.6 to 26)	NA
Education, y	14 (12 to 18)	16 (12 to 18)	0.45	16 (12 to 20)	16 (12 to 20)	0.87
Short Test of Mental Status (/38)	37 (35 to 38)	37 (35 to 38)	0.70	38 (31 to 38)	29 (3 to 38)	<0.001
Clinical Dementia Rating Sum of Boxes (/18)	0 (0 to 0)	0 (0 to 0.5)	0.38	0 (0 to 1)	5 (1.5 to 16)	<0.001

Abbreviation: bvFTD = behavioral variant frontotemporal dementia; MAPT = microtubule associated protein tau.

^a Data shown as median (range) unless otherwise stated.

^b Years before expected symptom onset (calculated using average symptom onset in each family).

mixed results, with atrophy and hypometabolism observed in some asymptomatic subjects, but not others.^{11–15}

Resting-state fMRI has recently emerged as a sensitive biomarker to detect changes in brain functional connectivity.^{16–18} Functional connectivity is altered in patients with bvFTD,¹⁹ with reduced connectivity observed in the salience network that plays a role in processing social-emotional and homeostatically relevant stimuli,²⁰ and increased connectivity in the anti-correlated default mode network (DMN), involved in episodic memory function.¹⁸ It has been proposed that changes in functional connectivity may precede the occurrence of atrophy,²¹ and may therefore constitute one of the earliest features of the disease.

We aimed to determine whether functional connectivity is altered in asymptomatic *MAPT* subjects, and to compare changes to those observed in clinically diagnosed bvFTD.

METHODS Subjects. We identified all subjects seen at Mayo Clinic, Rochester, MN, between January 2009 and July 2010 who had screened positive for mutations in *MAPT*, were asymptomatic, and had a volumetric MRI and resting-state fMRI scan. Eight subjects, from 4 families, were identified, including 3 with the N279K (c.1842T>G; p.Asn279Lys) mutation from a pallido-ponto-nigral degeneration (PPND) family,²² 3 with the V337M (c.2014G>A; Val337Met) mutation, 1 with the P301L mutation (c.1907C>T; p.Pro301Leu), and 1 with the R406W (c.2221C>T; p.Arg406Trp) mutation. All subjects had been enrolled and followed prospectively with annual clinical examinations. None of these subjects have yet developed any symptoms of bvFTD or any other neurodegenerative disease. Eight subjects who had screened negative for mutations in *MAPT* and were cognitively normal were identified and used as a control group (referred to as *MAPT* controls). These subjects were members of 3 families that had screened positive for mutations in *MAPT*.

We also identified 21 subjects seen at Mayo Clinic, Rochester, MN, who fulfilled clinical criteria¹ for a diagnosis of bvFTD and had a volumetric MRI and a resting-state fMRI scan. Of these, 4 had mutations in *MAPT* (1 with the P301L mutation [c.1907C>T; p.Pro301Leu] and 3 with the V337M mutation [c.2014G>A; Val337Met]). These 21 subjects were age and gender-matched to 21 healthy control subjects (referred to as bvFTD controls). Subject demographics are shown in the table.

Standard protocol approvals. Informed consent was obtained from all subjects for participation in the studies, which were approved by the Mayo institutional review board.

Genetic analysis. Analysis of *MAPT* exons 1, 7, and 9–13 was performed using primers and conditions that were previously described.⁵ PCR amplicons were purified using the Multiscreen system (Millipore, Billerica, MA) and then sequenced in both directions using Big Dye chemistry following manufacturer's protocol (Applied Biosystems, Foster City, CA). Sequence products were purified using the Montage system (Millipore) prior to being run on an ABI 3730 DNA Analyzer. Sequence data were analyzed using either SeqScape (Applied Biosystems) or Sequencher software (Gene Codes, Ann Arbor, MI).

Image acquisition. A standardized protocol was performed on a 3T GE scanner. The resting-state fMRI signal time series was acquired using a gradient echoplanar sequence (repetition time [TR]/echo time [TE] = 3,000/30 msec, 90° flip angle, slice thickness 3.3, and 103 volumes). Subjects were instructed to keep their eyes open during scanning. A 3-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) was also acquired (TR/TE/inversion time, 2,300/3/900 msec; flip angle 8°, 26-cm field of view [FOV]; 256 × 256 in-plane matrix with a phase FOV of 0.94, slice thickness of 1.2 mm). All MPRAGE images underwent preprocessing correction for gradient nonlinearity and intensity nonuniformity.²³

Processing of resting-state fMRI. Preprocessing and data analysis were performed utilizing SPM5 and the resting-state fMRI data analysis toolkit (REST) (<http://www.restfmri.net>).²⁴ Preprocessing steps included discarding the first 3 volumes to obtain steady state magnetization, realignment, slice time correction, normalization to template, smoothing with 4-mm full width at half maximum Gaussian kernel, linearly detrending to correct for signal drift, and 0.01–0.08 Hz bandpass filtering to reduce non-neuronal contributions to blood oxygenation level-dependent (BOLD) fluctuations. In addition, regression correc-

tion for spurious variables included rigid-body transformation motion effects, global mean signal, white matter, and CSF.^{17,25} These preprocessed images were first analyzed using group independent component analysis (ICA) and dual regression in order to identify the DMN and salience network. The ICA analysis was performed using the asymptomatic *MAPT* subjects and *MAPT* controls since this was the comparison of primary interest. The results of the ICA were then used to select seeds for a seed-based connectivity analysis of each network.

ICA analysis. Independent components were identified using model-free ICA (MELODIC)²⁶ with a low-dimensional estimation of 20 independent components. The DMN and salience network were identified by visual inspection. Individual ICNs were then derived for all subjects utilizing spatial and temporal dual regression, and individual components were entered into statistical analysis. One-sample *t* tests were used to display voxelwise connectivity maps in the *MAPT* controls for each network with results assessed at $p < 0.05$ corrected for multiple comparisons using familywise error (FWE) at the cluster level.

Seed-based analysis. The results of the ICA one-sample *t* tests of the DMN and salience networks were used to select seed regions of interest (ROIs) for the voxelwise connectivity analysis. We selected the voxel with the highest *T* score in the precuneus to represent the DMN network (MNI coordinates 0, -60, 27). Since the fronto-insular cortex is a critical salience network hub,²⁷ we selected the voxel with the highest *T* score in the fronto-insular cortex to represent the salience network (MNI coordinates 54, 9, 3). Although the ICA was based on the younger *MAPT* subjects and controls, the seed locations remained identical when the ICA was run with the bvFTD controls. A 6-mm seed was placed for each location. The average BOLD signal time course within each seed was correlated to every voxel in the brain for each subject in the study using Pearson correlation coefficient. The correlation coefficients were converted to *z* scores using the Fisher *r*-to-*z* transformation. Voxels that have positive *z* scores relative to the seed time courses indicate “in-phase” connections and the voxels with negative *z* scores indicate “out-of-phase” connections. These *z* score images were entered into the statistical analysis.

Two-sample 2-sided *t* tests were performed to compare voxelwise connectivity between 1) asymptomatic *MAPT* subjects and *MAPT* controls, 2) subjects with bvFTD and bvFTD controls, and 3) asymptomatic *MAPT* subjects and subjects with bvFTD. These analyses were performed for both the DMN and salience networks. In order to assess only in-phase connections the group comparisons were masked by the out-of-phase connectivity map identified in a one-sample *t* test of the matched control group. Results were assessed at $p < 0.05$ corrected for multiple comparisons using FWE at the cluster level, and age and gender were included in the models as covariates. In addition, functional connectivity was assessed across specific ROIs defined using the AAL atlas.²⁸ ROIs were placed to sample areas that showed altered functional connectivity in the disease groups (see Results). Therefore, DMN ROIs were placed in lateral temporal lobe, medial prefrontal cortex, and medial parietal lobes (precuneus + posterior cingulate), and a salience ROI was placed in anterior cingulate.

Processing of structural MRI. Voxel-based morphometry using SPM5 was used to assess patterns of gray matter loss in the asymptomatic *MAPT* subjects compared to *MAPT* controls and in the subjects with bvFTD compared to bvFTD controls. Image processing was performed as previously described,²⁹ and anal-

yses were assessed corrected for multiple comparisons using the false discovery rate ($p < 0.0005$) with age and gender included as covariates. Atlas-based parcellation using the AAL atlas was used to generate gray matter volumes for each of the regions assessed in the fMRI analysis, as previously described.²⁹ Total intracranial volume (TIV) was also calculated and used to correct regional gray matter volumes for differences in head size.

Statistics. Subject demographics were compared between groups using χ^2 tests and Wilcoxon rank sum test. For group comparisons of ROI-level data, we used analysis of covariance models, in which the ROI measurement was the response, age at imaging was an adjustment covariate, and group was a 2-level predictor. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria).

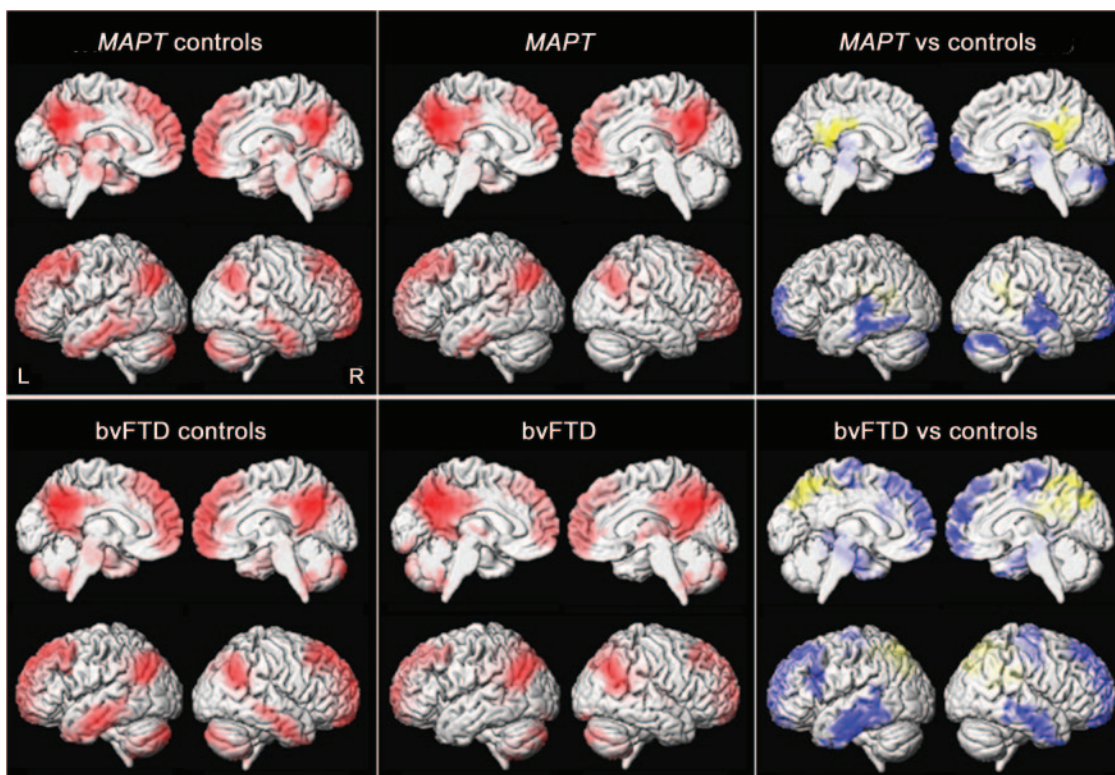
RESULTS Default mode network (precuneus seed).

The precuneus seed showed in-phase connectivity with medial and lateral parietal lobe, medial prefrontal cortex, and lateral temporal lobe in controls (figure 1). The asymptomatic *MAPT* and bvFTD groups showed reduced in-phase connectivity in lateral temporal lobes and medial prefrontal cortex compared to controls (figures 1 and 2). The bvFTD group also showed reduced connectivity in dorsolateral frontal lobe. Increased in-phase connectivity was observed in both groups in medial parietal lobe. The asymptomatic *MAPT* group showed greater reduction in connectivity in lateral temporal lobe and basal ganglia than subjects with bvFTD (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). The subjects with bvFTD did not show any regions of reduced connectivity compared to asymptomatic *MAPT* subjects.

Salience network (fronto-insular cortex seed). The fronto-insular cortex seed showed in-phase connectivity predominantly with bilateral fronto-insular cortex, anterior cingulate, and dorsolateral frontal lobes in controls (figure 3). In SPM, only the subjects with bvFTD showed alterations in this pattern, with reduced in-phase connectivity in bilateral fronto-insular cortex, anterior cingulate, dorsolateral frontal lobes, and striatum (figures 2 and 3). The asymptomatic *MAPT* subjects did, however, show a trend at the ROI level for reduced connectivity in anterior cingulate (figure 2). No regions showed increased connectivity in either group and no differences were observed between the asymptomatic *MAPT* subjects and subjects with bvFTD.

Gray matter loss. The subjects with bvFTD showed a widespread pattern of gray matter loss involving temporal, frontal, and parietal lobes compared to the bvFTD controls (figures 2 and 4). No gray matter loss was identified in the asymptomatic *MAPT* subjects compared to the *MAPT* controls (figure 2 and 4).

Figure 1 Resting-state fMRI results from the default mode network seed-based analysis of the precuneus



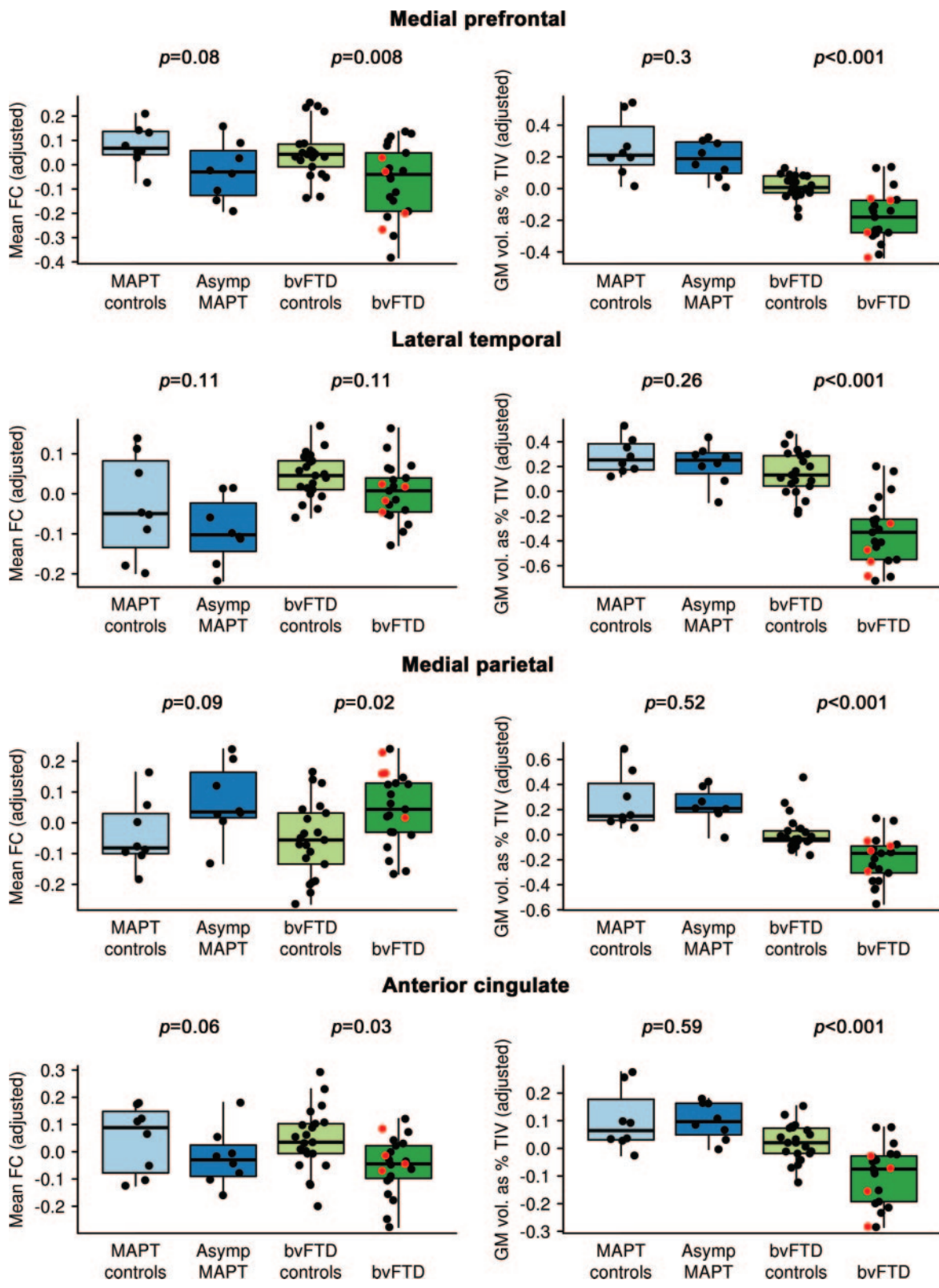
The top row shows the results for the asymptomatic *MAPT* subjects and the *MAPT* controls, while the bottom row shows the results for the subjects with behavioral variant frontotemporal dementia (bvFTD) and the bvFTD controls. Left: Patterns of in-phase voxelwise connectivity observed in control subjects. Middle: Patterns of in-phase voxelwise connectivity observed in the disease groups. Right: Patterns of reduced (shown in blue) and increased (shown in yellow) in-phase connectivity in the disease groups compared to the age-matched controls. Results are shown after cluster-level correction for multiple comparisons at $p < 0.05$.

DISCUSSION We have demonstrated that functional connectivity in the brain is altered in subjects with mutations in *MAPT* even before the occurrence of gray matter atrophy and clinical symptoms. These findings increase our understanding of disease progression and suggest that changes in functional connectivity could be one of the earliest features of the disease.

The asymptomatic *MAPT* subjects showed reduced connectivity in the DMN predominantly between precuneus and lateral temporal lobe, but also medial prefrontal cortex, compared to age-matched controls. Gray matter loss has been observed in these regions in symptomatic *MAPT* subjects, with particularly severe involvement of the temporal lobes.^{9,10} However, no gray matter loss was observed in these regions in the asymptomatic subjects, suggesting, importantly, that changes in functional connectivity precede the occurrence of atrophy in these regions. Very similar patterns of reduced DMN functional connectivity were observed in bvFTD, involving both lateral temporal lobes and medial prefrontal cortex, again suggesting that these patterns are disease-related.

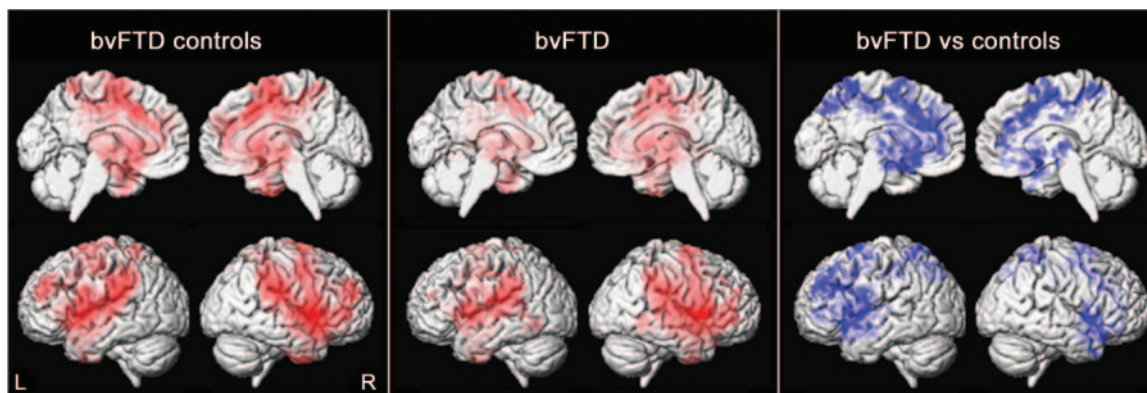
While the posterior DMN has been associated predominantly with episodic memory and visuospatial functions which are typically spared in bvFTD,¹ components of the DMN, such as medial prefrontal cortex and lateral temporal lobes, have been shown to be associated with functions such as semantic memory³⁰ and theory of mind,³¹ which show abnormalities both in subjects with bvFTD^{29,32} and *MAPT* subjects.⁶ It is therefore possible that deficits in the DMN could be responsible for some of the clinical features observed in bvFTD. The bvFTD group showed greater involvement of the frontal lobes, perhaps suggesting that disconnection of parietal and frontal lobes may relate directly to the development of behavioral symptoms. Our results contrast with a previous study that did not observe reduced DMN connectivity in bvFTD, and suggested that reduced DMN connectivity was a feature of Alzheimer disease (AD).¹⁹ However, given the similarity in the connectivity pattern between *MAPT* and bvFTD, and the fact that AD pathology is very unlikely in young individuals with *MAPT* mutations, we believe our findings are likely a feature of the primary tauopathy and not a manifestation of covert AD pa-

Figure 2 Box plots showing the distribution of mean functional connectivity (FC) and total intracranial volume-corrected gray matter (GM) volumes for the 4 regions of interest



Data are plotted separately for each of the 4 subject groups. Partial residuals from the analysis of covariance model are plotted. The value on the y-axis can be interpreted as the observed value minus what would be expected under the model given the subject's age. The boxes indicate the 25th, 50th (median), and 75th percentiles of the distributions while the horizontal lines extending from the boxes stop at the most extreme data points. The p values indicate the significance of differences between the asymptomatic MAPT subjects and their age-matched controls, and between the subjects with behavioral variant frontotemporal dementia (bvFTD) and their age-matched controls, using the Wilcoxon rank sum test. Four of the subjects with bvFTD had mutations in MAPT (shown in red).

Figure 3 Resting-state fMRI results from the Salience network seed-based analysis of the fronto-insular cortex



Results are shown only for the behavioral variant frontotemporal dementia (bvFTD) comparisons, since no significant changes in functional connectivity were observed in the asymptomatic *MAPT* subjects. Left: Patterns of in-phase voxelwise connectivity observed in the bvFTD control subjects. Middle: Patterns of in-phase voxelwise connectivity observed in the subjects with bvFTD. Right: Patterns of reduced (shown in blue) and increased (shown in yellow) in-phase connectivity in the subjects with bvFTD compared to the age-matched controls. Results are shown after cluster-level correction for multiple comparisons at $p < 0.05$.

thology. Discordance across the studies may be due to methodologic differences or inclusion of different anatomic subtypes of bvFTD.²⁹

In contrast to the DMN findings, reduced functional connectivity in the salience network was a more striking feature of bvFTD rather than asymptomatic *MAPT*. Reduced connectivity was observed between the fronto-insular cortex seed and surrounding fronto-insular cortex and anterior cingulate in bvFTD. These reductions in the salience network are similar to those previously reported in bvFTD.¹⁹ The SPM analysis failed to identify any regions of reduced salience connectivity in the asymptomatic *MAPT* subjects, although there was a suggestion of reduced connectivity in anterior cingulate at the ROI level. The less striking findings in this group concur with the finding that *MAPT* mutations are associated with predominant temporal lobe involvement, with less involvement of frontal regions that are considered part of the salience network.^{9,10} Behavioral deficits that occur in symptomatic *MAPT* subjects could be due to deficits in the right temporal lobe.³³

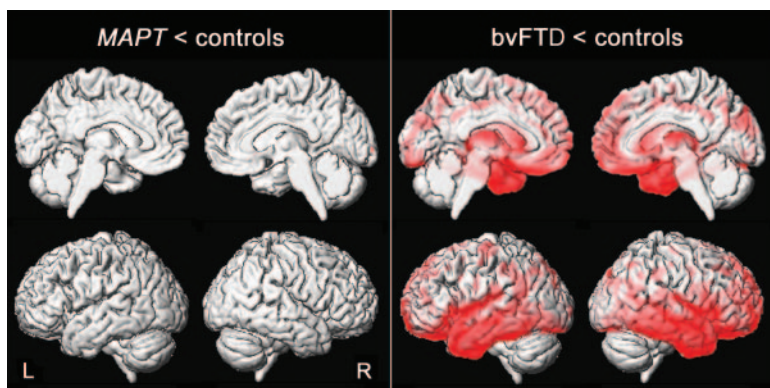
Increased functional connectivity was also observed in medial parietal regions of the DMN in both the asymptomatic *MAPT* subjects and subjects with bvFTD. This enhancement in posterior regions of the DMN has previously been observed in bvFTD and has been shown to be associated with reduced connectivity in the anti-correlated salience network.¹⁹ Impairment in the salience network is thought to alter the posterior DMN responses leading to enhanced parietal lobe functions.¹⁹ Our bvFTD findings concur with this hypothesis, although the asymptomatic *MAPT* subjects did not show strong reciprocal reductions in the salience

network. This could suggest that the temporal sequence of events is reversed in *MAPT* subjects, with changes in the DMN occurring before the salience network. Alternatively, our sensitivity to detect network abnormalities could also be greater in the DMN.

Gray matter atrophy was observed in all regions that showed reduced functional network connectivity in bvFTD, suggesting an association between these 2 mechanisms. However, somewhat counterintuitively, we observed parietal lobe atrophy yet functional connectivity increases in bvFTD. Since parietal lobe is not commonly an early site of pathologic damage in bvFTD,³⁴ atrophy is largely due to spreading of disease from the pathologically damaged frontal and temporal lobes.³⁴ Increased functional connectivity in this region is likely due to a disconnection from pathologically affected salience regions. Therefore, atrophy and increased functional connectivity in this region may be resulting independently from pathologic changes occurring elsewhere in the brain.

The similarity of findings in the asymptomatic *MAPT* subjects to the bvFTD group provided an important validation of the results. A limitation, however, was that the bvFTD group did not consist solely of subjects with mutations in *MAPT*, and therefore cannot be strictly considered as being on the *MAPT* disease spectrum. Subjects with bvFTD have heterogeneous pathologic and genetic etiologies,² which are typically associated with differing patterns of atrophy.^{10,35} Patterns of functional change in bvFTD may also differ according to pathology or genetics, although without pathologic confirmation we cannot draw firm conclusions concerning any such relationships. The 4 subjects with bvFTD with mutations in *MAPT* did however show very similar

Figure 4 Patterns of gray matter loss in the asymptomatic *MAPT* subjects and the subjects with behavioral variant frontotemporal dementia (bvFTD) when compared to their age-matched controls



Results are shown on 3-dimensional renderings of the brain after correction for multiple comparisons using the false discovery rate at $p < 0.0005$.

patterns of functional change to the rest of the bvFTD cohort.

The strengths of our study include the fact that the asymptomatic *MAPT* subjects and subjects with bvFTD were each matched to a control group that was as close as possible in age, and age was included in all analyses as a covariate to further reduce potential confounds. Functional connectivity alters during aging,^{36–38} and indeed we observed age-related differences in the lateral temporal lobe. The *MAPT* controls all screened negative for mutations in *MAPT*, but were from families that had screened positive, allowing us to inherently match for other genetic features. The number of subjects with *MAPT* mutations was however relatively small compared to the bvFTD group; this could have contributed to the negative findings and borderline ROI p values in this group. While resting state fMRI has an advantage over task-related fMRI in eliminating performance confounds, there are still some methodologic issues that need to be resolved.³⁹ One key issue is the interpretability of out-of-phase correlations between regions introduced due to global signal removal.

The findings from this study have important implications for the study of FTD. They suggest that disruptions in functional connectivity may be a fundamental and critical early stage in the disease. Future studies, with larger numbers of subjects, test-retest assessments, and longitudinal imaging, will be needed to determine if functional connectivity fulfills criteria to be an early biomarker in FTD.

AUTHOR CONTRIBUTIONS

Dr. Whitwell: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of the data, acquisition of data, statistical analysis. Dr. Josephs: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of the data, acquisition of data, study supervision. Dr. Avula: drafting/revising the manuscript for

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DISCLOSURE

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Neurology

Historical Abstract: May 1, 1967

PARKINSONISM: ONSET, PROGRESSION, AND MORTALITY

MM Hoehn, MD Yahr

Neurology 1967;17:427-442

Parkinsonism, described in its entirety over one hundred and fifty years ago,¹ rarely presents itself as a diagnostic problem. In consequence, little scrutiny has been directed to the marked variability of this frequently encountered neurological syndrome and to the progression of the disease in large groups of patients. As with most chronic neurological disorders, marked diversity can be expected to exist in age and mode of onset, relative prominence of the cardinal signs and symptoms, rate of progression, and resultant degree of functional impairment. Controversy over the effectiveness of therapeutic measures for parkinsonism is due partially to this wide variability and to the paucity of clinical information about the natural history of the syndrome. It is also related to differences in terminology regarding the type of parkinsonism and the degree of its severity at the time of treatment. Consequently, it is difficult to determine whether treatment really influences the course of the disease and to what extent symptomatic relief is significant. It seems clear that, at a time when many new approaches to the treatment of parkinsonism are being suggested, information of this sort is of paramount importance.

References can be found in the online article.

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Comment from Ryan J. Uitti, MD, FAAN, Associate Editor: *The first large longitudinal experience of a syndrome, parkinsonism, this landmark paper not only described expectations regarding onset, progression, and mortality, but also provided the first staging system for parkinsonism. The modified Hoehn and Yahr staging system continues to be utilized by clinicians and researchers, reflecting upon the importance of this publication authored by outstanding clinicians from two generations. The timing of the article, reporting experience from the pre-levodopa era, allowed one last glimpse at expectations for this condition prior to meaningfully effective therapy.*