Title

Progression in behavioural variant frontotemporal dementia: a longitudinal study

Running Title

Progression in frontotemporal dementia

Authors and Affiliations

[1,2,3,] E. Devenney, [1] L. Bartley, [1] C. Hoon, [1,2,3] C. O'Callaghan, [1,2,4] F. Kumfor, [1,5] M. Hornberger, [1,2] J.B. Kwok, [1,2] G.M. Halliday, [1,2,4] M.C. Kiernan, [1,2,4] O. Piguet, [1,2] J.R. Hodges

[1]Neuroscience Research Australia, Sydney, NSW

[2]University of New South Wales, Sydney, NSW

[3]Brain and Mind Research Institute, Sydney, NSW

[4]ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia

[5]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Email and postal address of corresponding author

Dr Emma Devenney, Neuroscience Research Australia, Barker Street, Randwick, Sydney, NSW 2031. e.devenney@neura.edu.au

Character count

Title – 72; Running title – 35

Word Count

Abstract – 250; Introduction – 430; Discussion – 1499; Body of Manuscript - 4887

Tables – 6; Figures – 6; Colour figures - 5

Abstract

Objective: This study aimed to i) observe longitudinal outcomes and progression in behavioural variant frontotemporal dementia, with respect to probable and possible behavioural variant frontotemporal dementia, in accordance with international diagnostic criteria and ii) identify features that may aid clinicians better prognosticate in cases of possible behavioural variant frontotemporal dementia.

Methods: We followed 58 consecutive patients longitudinally over a 6-year period and classified these patients as possible, probable or definite behavioural variant frontotemporal dementia, at presentation and latest review. Clinical, pathology, genetic, neuropsychological and neuroimaging data were analysed to categorise patients, compare group differences, determine rates of progression and identify prognostic features in possible bvFTD.

Results: At presentation, 38 patients fulfilled probable criteria and of these, 36 remained probable or converted to definite over time. The remaining 20 patients satisfied possible criteria only and greater than one-half changed category over time, termed changers, and progressed on cognitive and functional measures. Most (eight, 40%) of these harboured the *C9orf72* expansion. A positive family history, memory impairment and clinical abnormalities at presentation appeared as key features of progression ($p < 0.05$). A continuum of neuropsychological scores, progression rates and atrophy severity emerged across patients in probable, possible, changer and non-changer categories, with probable bvFTD patients exhibiting the most severe abnormalities.

Interpretation: Behavioural variant frontotemporal dementia can show variable progression over time. A detailed neurological assessment may identify key features of progression when faced with the difficult case of possible bvFTD, while a diagnosis of probable bvFTD is accurate in a clinical setting.

Introduction

The past two decades have seen a revolution in the characterization of behavioural variant frontotemporal dementia (bvFTD), which culminated in the development of internationally accepted diagnostic consensus criteria for bvFTD in 2011 [1]. These criteria segment the diagnosis of bvFTD into three tiers of certainty; possible, probable and definite according to neuroimaging, genetic and pathological findings. These criteria correctly classified 90% of all bvFTD cases in a recent large clinicopathological study [2].

Despite this progress, prognosis of bvFTD remains challenging. A number of patients without atrophy on MRI only satisfy criteria for possible bvFTD, and remain in this category for years. Some of these patients are described as 'phenocopy' cases; the hallmark features of which include normal neuroimaging, preserved activities of daily living, normal ability on a battery of cognitive tasks and lack of progression [3-6]. In the absence of pathological reports of phenocopy cases the underlying neuropathological changes remain unknown.

The discovery of the *C9orf72* genetic expansion added a level of complexity to the bvFTD diagnosis. Indeed, in the absence of genetic testing, many patients harbouring this gene expansion satisfy the diagnostic criteria for possible, but not probable bvFTD at first presentation. The wealth of case reports emerging, detailing protracted and indolent cases with apparently normal neuroimaging and relatively normal neuropsychological profiles, are testament to the complex nature of this expansion [7-9]. It is not surprising that a number of these patients were considered to be 'phenocopy'. So while considerable refinements in diagnostic criteria have been made, pieces of the

puzzle remain – how do we deal with 'possible bvFTD'; how many 'possible bvFTD' cases evolve to probable or definite disease; and where does the *C9orf72* expansion fit into current diagnostic criteria.

With these questions in mind, the present study explored the outcomes in a large bvFTD cohort. Drawing on previous clinicopathological studies in bvFTD, we hypothesised that the majority of probable cases in the study would remain probable or become definite on the basis of post-mortem examination [10, 11]. Possible bvFTD as a separate entity has not yet been studied, however we expected some to exhibit deficits on neuropsychological measures sensitive to frontal lobe dysfunction, in keeping with true bvFTD. Contrary to the recommendations of the international diagnostic criteria and in line with recent evidence that bvFTD patients experience a degree of amnesia we suspected that many of our patients would also exhibit memory deficits [12].

This longitudinally recruited cohort is ideal to address these issues as each participant was subject to a detailed work-up that included comprehensive clinical assessment, neuropsychological test battery, neuroimaging, genetic testing and long-term follow-up.

Methods

Patients

Each patient was assessed at FRONTIER Frontotemporal Dementia Research group between 2008 and 2013. Patients were included in the study if they satisfied criteria for possible, probable or definite bvFTD and if they were seen on at least two occasions over a two-year period or more to allow time for significant progression, or (2) seen over a one-year period with a change in diagnosis over this period [1]. Patients with FTD and concurrent Motor Neuron Disease (FTD-MND) were excluded from the study, but those who developed MND as their disease progressed were included.

Ethical approval for this study was obtained from the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. Participants, or their person responsible, provided informed written consent in accordance with the Declaration of Helsinki.

Patients were classified as possible, probable or definite bvFTD according to international diagnostic criteria [1]. The diagnosis was reviewed on two occasions: at presentation and most recent attendance. To meet possible bvFTD criteria three of six core behavioural features were present namely disinhibition, apathy, loss of sympathy/empathy, stereotyped/compulsive behaviors, a change in dietary preference towards sweet foods and a frontal dysexecutive cognitive profile with relative sparing of memory and visuospatial function. To reach probable bvFTD, criteria for possible was met with additional evidence of functional decline, as well as frontal or temporal abnormalities on MRI or Fludeoxyglucose (18F)-Positron emission topography. For the purpose of classification and to determine if atrophy was present, MRI scans were reviewed using a validated visual rating scale, which assessed the orbitofrontal cortex, anterior temporal poles and insular cortex according to previously published data [13, 14]. Atrophy was rated on a Likert scale by a blinded rater (ED) after appropriate training

on an independent data set. Intra-class correlation coefficient to assess inter-rater reliability was very high (Cronbach's alpha = .9). The scale ranged from 0 (no atrophy) to 4 (severe atrophy). A score of 0-1 denoted normal brain while 2-4 was considered abnormal. The criterion for 'definite bvFTD' stipulate that pathological findings at autopsy, or genetic findings during life must confirm the diagnosis. All patients underwent genetic testing for the *C9orf72* expansion and then those with a negative result but with a positive family history were tested for the *microtubule associated tau protein* (MAPT) and *progranulin* (GRN*)* genetic mutations. Each patient was offered the opportunity to join the FRONTIER brain donor programme. Pathological evidence from all such brain donors who died during the period of the study was analysed and included in the present study.

Clinical assessment

Patients were assessed by an experienced behavioural neurologist and clinical information was recorded on a standardized proforma. Behavioural symptoms were systematically explored during the carer interview based upon the CBI (Cambridge Behavioural Inventory) [15] and corroborated by the carer based responses on the Neuropsychiatric Inventory (NPI) [16] which was completed prior to the visit. Neurological examination documented features of MND, aphasia, Parkinsonism, apraxia, ataxia and eye movement abnormalities.

A family history was obtained and the Goldman score was calculated [17]. A score of 1 = at least three family members affected with diagnosed FTD and or MND over two generations with one person being a first degree relative of the other; 2 = three

or more family members affected with dementia and/or MND but do not meet criteria for 1; 3 = at least one affected family member with confirmed FTD and/or MND or early onset dementia; 3.5 = one affected relative with unspecified or late onset dementia; 4 = no family history. A score of 3 or below was considered a positive family history. A family history of significant psychiatric illness in first-degree relatives was also obtained. A significant family history was considered present if a psychiatric diagnosis (e.g. schizophrenia, schizotypal, delusional disorder, mood disorder) was made by a trained psychiatrist and was sufficient to require treatment and or impacted on functional ability.

Global cognitive function was measured using the Addenbrooke's Cognitive Examination-Revised (ACE-R;[18]. Disease staging was assessed with the Frontotemporal Dementia Functional Rating Scale (FRS) [6].

Neuropsychological assessment

The cognitive assessment examined the integrity of the main cognitive domains, as well as emotion processing capacity. Episodic memory was tested using the delayed recall components of the Rey-Osterrieth Complex Figure test [19, 20] and the Rey Auditory Verbal Learning Test [21]. Visuospatial ability was measured with the copy component of the Rey-Osterrieth Complex Figure test [19, 20]. Working memory and executive functions were measured with the Digit Span Backwards test [22], the Hayling test of inhibitory response [23], Verbal Fluency (FAS) [24] and the Trail Making Test [25]. Naming was assessed using the Sydney Language Battery

(SYDBAT) [26]. Finally, emotion processing was assessed using The Awareness of Social Inference Test (TASIT) [27] and the Ekman 60 [28]

Analysis of group differences on behavioural, clinical and neuropsychological measures

Data was compared between 1) the entire bvFTD group and controls, 2) probable bvFTD and possible bvFTD and 3) possible bvFTD patients who became probable/definite, termed *changers*, and possible bvFTD cases who remained possible, termed *non-changers*. Age-matched healthy controls (n = 25) were selected from the FRONTIER voluntary control database.

Genetic screening

DNA was extracted from whole blood collected for genetic screening following informed consent and using protocols approved by the Human Research Ethics Committee of the South Eastern Sydney and Illawarra Area Health Service. The repeat primed PCR was performed using the procedure described previously [29], based on the protocol of Renton and colleagues [30]. A patient's DNA sample was deemed positive for the *C9orf72* repeat expansion if it contained an allele with > 30 repeats. Patients with a family history were also screened for other common genetic mutations (GRN, MAPT) by Sanger sequencing of genomic DNAs corresponding to all coding exons [31, 32]

Neuropathology

Consent for brain donation for research was obtained for each case with tissue collection and processing performed by the Sydney Brain Bank according to protocols approved by the Human Research Ethics Committee of the University of New South Wales. Cases were systematically classified into the major molecular classes of frontotemporal lobar degeneration [FTLD-tau, FTLD-TDP (FTLD-transactive response DNA binding protein of 43 kDa), FTLD-FUS (FTLD-fused in sarcoma), FTLD-UPS (FTLD-ubiquinated inclusion bodies) and FTLD-ni (FTLD without inclusions)][33] in addition to criteria for other neurodegenerative disorders [34] using immunohistochemical techniques [35].

Neuroimaging

Imaging acquisition

All participants underwent whole-brain T1 imaging using a 3T Philips MRI scanner with standard quadrature head coil (eight channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, $1mm^2$ in-plane resolution, slice thickness 1mm, echo time/repetition time = 2.6/5.8 ms.

Voxel-based morphometry analysis

Three-dimensional T1-weighted sequences were analysed with FSLVBM, a VBM analysis [36] and part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html. Tissue segmentation was carried

out using FMRIB's Automatic Segmentation Tool (FAST) from brain-extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI 152) using the non-linear registration approach using FNIRT, which uses a b-spline representation of the registration warp field. The registered partial volume maps were divided (to correct for local expansion or contraction) by the Jacobian of the warp field. These images were smoothed with an isotropic Gaussian kernel with a standard deviation of 3mm (full-width at half-maximum: 8mm). A voxel-wise general linear model was applied and permutation-based non-parametric testing was used to form clusters with the Threshold-Free Cluster Enhancement method, tested for significance at <0.01 corrected for contrasts between bvFTD cohorts with a cluster-extent threshold of at least 50 contiguous voxels. A more lenient threshold was used for subgroup analysis (< 0.05 corrected for patient subgroup versus controls and < 0.01 uncorrected for between patient group comparisons) to increase the statistical power. Contrasts were corrected for Family wise error (FWE).

Statistical analysis

Data were analysed using SPSS 22.0 statistical package. Kolmogorov-Smirnoff tests were applied to determine if variables were normally distributed. Parametric variables were compared across groups via independent t-tests and analysis of variance (ANOVA). Non-parametric data were analysed using Mann-Whitney and the Kruskal-Wallis tests, and categorical data were compared with Chi-Square tests. Linear mixed effects models were built to examine the change in performance across groups, over time [37].The fixed effects of the model included

diagnostic category, follow-up time (calculated as days from first ACE-R assessment) and the interaction between diagnostic category and follow-up time. The only random effect modeled was the individual variability associated with the participants at baseline, using the random intercept model. A significant effect of follow-up time indicates that performance on the variable of interest changes linearly over time, averaged across groups. A significant interaction between diagnostic category and follow-up time indicates that the rate of change (slope) differs according to diagnosis.

Results

Participants, genetics and neuropathology – the entire bvFTD cohort

Of 89 patients with bvFTD who were seen at the clinic over the study period, 58 met inclusion criteria. Of the 31 patients who failed to meet inclusion criteria, due to lack of sufficient follow-up, 12 were probable cases and 19 were possible bvFTD cases. The 12 probable cases had either passed away without autopsy or were too severely impaired for follow-up. Of the 19 possible cases five had moved to a distant location and 14 were uncontactable many of whom had complex family issues when seen at first presentation. Follow-up ranged from 1 to 5.2 years with a mean follow-up period of 3.1 years. Demographic data are represented in Table 1.

The *C9orf72* expansion was present in 15 patients, representing 30% of the entire cohort. Based on the Goldman score, a positive family history was present in 18

(31%) of the total cohort (Table 2). Of these familial cases, the *C9orf72* expansion was present in 10 (55%), a *GRN* mutation in five (28%) and a *MAPT* mutation in one (6%). Known genes were not present in two familial cases (11%). Five patients with apparently sporadic disease, representing 12.5% (five of 40) of the sporadic cases harbored the *C9orf72* expansion. Three of these patients had a positive family history of significant psychiatric disease, which was present in six (40%) of the entire *C9orf72* cohort. When the diagnostic criteria for bvFTD were applied, 20 met criteria for possible bvFTD and 38 patients met criteria for probable bvFTD.

** Insert (Table 1) here

Of the 38 probable cases, almost a half (17, 47%) became definite at follow-up, while a half (19, 50%) remained probable at follow-up and two (6%) had confirmed Alzheimer's disease pathology at autopsy (Figure 1). *C9orf72* expansions were found in both familial (n = 5) and sporadic disease (n = 2). A family history of psychiatric disease was present in one of two patients with apparently sporadic disease. In two of 13 (15%) familial cases, no known gene was found. Three probable cases developed clinical and neurophysiological evidence of MND.

In the possible bvFTD group, failure to meet criteria for probable bvFTD at presentation was due to a lack of imaging abnormalities, based on the visual atrophy rating scale and FDG-PET in all cases. Each patient displayed a degree of functional decline. Among the 20 possible bvFTD cases at baseline, 11 changed category over time to become probable or definite cases (labeled here 'changer'; Figure 1). Of these, eight (80%) were found to harbour the *C9orf72* gene expansion, five of these had a positive family history of dementia. In other words, all five patients with a positive family history in the 'changer' group harboured the *C9orf72* gene expansion. Two of

the remaining three sporadic cases had a family history of psychiatric disease. The final three cases in the 'changer' group were diagnosed with 'probable bvFTD' following the development of brain atrophy on MRI. Mild to moderate brain atrophy on MRI was also observed in five of eight individuals with *C9orf72* expansion at follow-up. The remaining nine possible bvFTD cases at baseline remained in the same diagnostic category at follow up (here labeled as 'non-changer'). None of the bvFTD non-changers had a significant family history of neurodegenerative disorders.

** Insert (Figure 1) here.

Comparison of bvFTD and controls

Clinical and neuropsychological assessment

Abnormalities on clinical examination were present in over one-quarter of bvFTD patients and almost one-third had a positive family history. A detailed carer interview and NPI data revealed high rates of core behavioural symptoms in bvFTD participants. (Figure 2). BvFTD patients scored poorly across the range of neuropsychological tests compared to controls.

** Insert (Figure 2) here

Neuroimaging analysis – voxel-based morphometry atrophy analysis

Overall bvFTD patients showed widespread atrophy in the dorsolateral prefrontal cortex, temporal poles, insular cortex, thalamus and striatum based on VBM analysis

($p < 0.01$ corrected; Table 2). Atrophy was also present in posterior structures including occipital and parietal regions as well as the cerebellum.

** Insert (Table 2) here

Comparison of probable and possible bvFTD

Clinical assessment

Abnormal clinical findings on neurological examination were present in both probable (n=11) and possible (n=5) bvFTD patients ($p > 0.05$). The groups showed similar rates of family history positivity. Stereotypic/compulsive behaviours were more prevalent in the probable group ($p < 0.05$), while other behavioural features were similar across the groups (Figure 2).

Neuropsychological assessment

On a group level, probable bvFTD patients exhibited significantly poorer performance across all cognitive domains except for naming ($p > 0.1$), than possible bvFTD patients ($p < 0.05$; Table 3). Compared to controls both probable and possible bvFTD patients showed significant cognitive impairment.

**Insert (Table 3) here

Longitudinal data

On a measure of global cognitive function, the ACE-R, the groups combined showed significant deterioration over time ($p < 0.001$) with a significant interaction between disease group and time ($p < 0.05$) indicating a faster rate of decline in probable bvFTD compared to possible bvFTD (Figure 3). On a measure of functional disability, the FRS, the group as a whole showed significant deterioration over time ($p < 0.001$), however no significant interaction between disease group and time ($p <0.001$) was identified indicating a similar rate of decline in both groups.

**Insert (Figure 3) here

Neuroimaging – voxel-based morphometry atrophy analysis

Figure 4 demonstrates widespread atrophy in frontal regions including the dorsolateral prefrontal cortex, temporal lobes and subcortical structures in probable bvFTD compared to controls and corrected at $p < 0.01$. Posterior regions of the parietal and occipital cortex were also involved.

Possible bvFTD patients showed similar regions of atrophy with a number of clusters found in posterior and subcortical regions including the cerebellum. Comparison between probable and possible bvFTD showed more atrophy in the probable group in frontal and subcortical regions while there were no areas of significant atrophy in the converse (Table 4).

**Insert (Table 4) and (Figure 4) here

Comparison of changers vs. non-changers

Clinical assessment

Abnormal clinical findings on neurological examination were found in the changer group only ($p < 0.05$; Parkinsonism n = 3, frontal release signs n = 2). The groups differed on the presence of stereotypic/compulsive behaviours with changers showing more abnormal behaviour than non-changers ($p < 0.05$, Table 2). Based upon a Goldman score, five of the changers, all of whom carried the *C9orf72* mutation, had a positive family history of neurodegeneration (MND n = 4, FTD n = 1) in comparison to none of the non-changers ($p < 0.01$).

Neuropsychological assessment (Table 5)

Changers vs. controls

In comparison to controls, and in keeping with the bvFTD profile of cognitive function, the changers scored significantly worse across the range of cognitive tasks (all p values < 0.05).

Changers vs. non-changers

The groups differed on components of the ACE-R namely memory and the total ACE-R score ($p < 0.05$). The most striking difference between groups was in episodic

memory. All aspects of memory differed significantly between groups including visual, verbal and recognition memory with changers scoring significantly worse than non-changers ($p < 0.05$).

On some tests of executive function there was evidence for poorer performance in changers compared to non-changers but findings were inconsistent across tasks.

Visuospatial functioning, emotion processing and naming scores did not differ significantly between changers and non-changers ($p > 0.2$).

Non-changers vs. controls

The profile in non-changers versus controls was variable for executive tasks and emotion processing but the non-changers consistently scored in the control range across the memory indices.

** Insert (Table 5) here

Longitudinal data – Do the changers deteriorate over time?

As expected, on a measure of global cognitive function, the ACE-R, the groups combined showed significant deterioration over time ($p < 0.05$) with a significant interaction between disease group and time ($p < 0.05$) indicating a faster rate of decline in the changers compared to non-changers (Figure 5). Similarly on a measure of functional disability, the FRS, the group as a whole showed significant deterioration over time ($p < 0.001$) with a significant interaction between disease

group and time (p <0.001) indicating a faster rate of decline in the changers compared to non-changers. Notably, non-changers remained stable on both measures.

** Insert (Figure 5) here

Neuroimaging – voxel-based morphometry atrophy analysis

Figure 6 displays the patterns of atrophy at presentation in changers and non-changers in comparison to healthy control participants, corrected for Family Wise Error (FWE) at $p < .05$). The changers showed widespread atrophy predominantly in the anterior insula, striatum, orbitofrontal cortex and temporal poles with a left sided predominance (Table 6). These patterns of atrophy largely replicate those reported previously in bvFTD and *C9orf72* mutation carriers. In contrast the non-changers showed minimal frontopolar atrophy only, in comparison to controls. Given the small sample sizes we used a less conservative threshold for between patient group comparisons. Direct comparisons between changers and non-changers revealed greater thalamic, anterior right insula, hippocampal as well as dorsolateral prefrontal cortex volume loss in the changer group ($p < 0.01$ uncorrected), compared to non-changers.

** Insert (Table 6) and (Figure 6) here

Discussion

This novel study provides fresh insights into the progression of possible bvFTD over time. The results of this study show two distinct trajectories for possible bvFTD patients. The first group, referred to as changers, deteriorate cognitively and functionally over time and are likely to carry the *C9orf72* expansion, while the second group, termed non-changers, remain stable over a number of years. The chance at presentation of following either trajectory is almost 50:50 but a number of predictive features have been identified. Family history of neurodegeneration, clinical abnormalities on examination, stereotypic and ritualized behaviours, and deficits on the ACE-R are associated with progression, with memory deficits also emerging as a marker of progression. Our results indicate that the likelihood of progression may be determined during a routine neurological consultation by means of a detailed clinical interview, examination and a brief test of global cognition. Brain atrophy analyses show subtle but widespread cortical atrophy in changers when compared to non-changers, in keeping with true bvFTD in the changer group. Notably, a probable bvFTD diagnosis in the clinic is accurate. Finally, a continuum of neuropsychological and neuroimaging abnormalities are seen across probable bvFTD, possible bvFTD, changers and non-changers, with most severe changes seen in probable bvFTD.

To firstly consider the possible cases, one–third of the entire cohort fell into this category at presentation. They exhibit key behavioural features of bvFTD yet show little, or no, atrophy on MRI as judged using a visual rating scale. This raises the question of whether such patients have neurodegenerative conditions. Although the sample size is relatively small and validation in a larger independent centre is desirable, it is nonetheless striking that almost one half of all possible cases were

C9orf72 positive, and all possible cases with a family history of neurodegeneration carried this mutation. A positive family history together with abnormalities on clinical examination emerge as robust clinical indicators of progression in this group. A careful clinical history to unearth a family history of a neurodegenerative disorder, especially MND, clinical examination and cognitive evaluation could identify the majority of cases likely to progress, many of whom harbour the *C9orf72* mutation, and may guide clinicians to appropriately identify patients for referral to genetic services. It should be remembered that genetic testing is not always easily accessible for clinicians as hospital budgets may not accommodate genetic screening testing or laboratories may not have the technology. It is also notable that a half of cases with this mutation initially only met criteria for possible rather than probable bvFTD.

Memory, traditionally considered to be unimpaired in bvFTD, appears as a hallmark neuropsychological deficit in the changer group. Not only is memory impaired but the deficit spans a variety of memory components. This is perhaps testament to the true nature of neurodegeneration in this group. Memory impairment in bvFTD is not a new concept [12]. A recent study compared memory scores in patients with true bvFTD to 'phenocopy' cases [38]. Similar to our data they identified a number of memory measures to distinguish true bvFTD from 'phenocopy' cases. This has been further corroborated in a study that identified two distinct amnestic profiles in bvFTD; one with severe memory deficits comparable to Alzheimers disease and another with subnormal and normal memory scores [39]. Bearing in mind that the majority of changers harbored the *C9orf72* mutation it is compelling that previous studies comparing *C9orf72* and sporadic bvFTD linked memory problems to mutation carriers [40]. In another study memory deficits were found to be comparable in both sporadic and *C9orf72* bvFTD but the underlying neural correlates differed between

the groups [41]. Our data indicates that of all cognitive assessments memory tests may best distinguish possible cases likely to progress from those who will remain stable over a number of years. In contrast, performance on executive tasks appears more variable and does not discriminate changers from non-changers.

This raises the fundamental question: what is the underlying abnormality in the non-changers? They show mild deficits on tests previously found to be sensitive markers of bvFTD such as inhibitory control and emotion processing [42]. Previously patients with little or no progression over years and normal imaging have been referred to as 'phenocopy cases'[3-5]. These patients are predominantly male and present with a collection of behavioural features indistinguishable from true bvFTD. It has been hypothesized that this presentation represents a decompensated developmental disorder in the Asperger-Autism spectrum appearing in later life. The results from the present study may partly corroborate this theory as mild executive impairments are seen in both non-changers and patients on the Asperger's/Autism spectrum [43]. Similarly emotion recognition is impaired in non-changers and can also be altered in the Asperger's/Autism spectrum [44]. A comparison study between these two groups may shed further light on this concept but unfortunately was beyond the scope of this study. The lack of significant atrophy on imaging also appears to support these theories although little is known of the functional, pathological and neurochemical processes at play. It remains possible that a proportion of such cases may have a sporadic form of neurodegeneration with extremely slow progression although this seems unlikely.

On a neuroanatomical level, our data suggests that while non-changers do not exhibit clear atrophy on visual inspection of MRI, there is subtle but significant widespread

atrophy present. The atrophy pattern is similar to that found in typical bvFTD and involves regions involved in memory and executive tasks [45, 46]. The thalamus has been highlighted in *C9orf72* imaging studies and is a key component in memory with links to an extended hippocampal circuit. In keeping with other studies, our data identified significant thalamic atrophy in the changers that accords well with their cognitive profile. The disparity between atrophy seen on automated VBM group studies and visual inspection of individual scans is concerning. Given the barriers to developing a quantifiable measure of individual grey matter integrity, physicians would be advised to be aware of bvFTD in the presence of an apparently normal MRI. Clearly more sensitive but clinically applicable methods of detecting subtle brain atrophy are required.

Subgroup analyses reveal a disassociation in progression between functional and cognitive abilities in probable as compared to possible bvFTD. Despite a similar length of illness, probable bvFTD patients show worse cognitive deficits at presentation and progress more rapidly than possible bvFTD patients. In contrast, although the possible group was less functionally impaired at presentation, the two groups deteriorate at a similar rate. This may be explained by previous work which suggests that cognitive assessment alone does not account for disease severity and progression in bvFTD [6]. In contrast, there was a clear lack of progression in non-changers over time, coupled with a lack of atrophy on MRI at follow-up. Longitudinal neuroimaging studies but may offer insight into the impact of functional versus cognitive changes in bvFTD over time.

Turning next to probable bvFTD. Within our cohort the diagnostic accuracy for probable bvFTD was high. Keeping in mind that these results have been generated

from a specialist FTD centre, they nevertheless suggest that physicians can be confident when they diagnose probable bvFTD, if current diagnostic criteria are applied. It is unsurprising that despite having behavioural, executive and imaging findings in keeping with bvFTD that 12% of probable cases had Alzheimer's disease pathology at autopsy. The clinical overlap between bvFTD and Alzheimer's disease with predominant frontal lobe pathology has long been recognized. Unfortunately the ability to distinguish between the two during life can be difficult but may become easier as nuclear imaging identifying beta-amyloid in brain tissue becomes more widely available [47]. The need to make this distinction will become more pressing if pathology-based pharmacological therapy becomes available.

As in other studies of bvFTD, *C9orf72* is the most common gene abnormality and together with *GRN* and *MAPT* mutations account for the majority of familial disease. There remains, however, a minority of familial cases without a known gene defect while the *C9orf72* mutation is also present in a number of apparently sporadic cases. A locus on chromosome 16p12.1-q12.2 has been linked to familial cases of FTD, particularly FTD-MND cases, which are negative for any of the known genetic mutations, suggesting that this region may harbour another genetic mutation for FTD [48]. Previous studies have shown that familial psychiatric illness is associated with *C9orf72* [49, 50], and we have demonstrated that when familial mental health disorders are considered as evidence of neurodegeneration the majority of sporadic cases can be accounted for.

Together these results have repercussions for the reliability of current diagnostic criteria, which state that to conform to the cognitive profile of bvFTD there should be 'relative sparing of episodic memory'. Imaging abnormalities must also be present to

meet probable criteria. Contrary to current recommendations, this study and numerous others have found that memory deficits in bvFTD are often present and comprise an important component of the phenotype. Finally, important information can be gleaned from the routine neurological consultation and clinicians should consider this when faced with difficult questions of prognosis and referral for genetic testing.

Acknowledgements

The Sydney Brain Bank is supported by the National Health and Medical Research Council of Australia, the University of New South Wales, and Neuroscience Research Australia. Lauren Bartley is the brain donor coordinator.

Author Contributions

E. Devenney contributed to the study design, data collection and analysis, manuscript preparation, writing and review.

L. Bartley contributed to study design, data collection, manuscript preparation and review.

C. Hoon contributed to data collection, manuscript preparation and review.

C. O'Callaghan contributed to data analysis, manuscript preparation and review.

F.Kumfor contributed to data analysis, manuscript preparation and review.

M. Hornberger contributed to study design, data analysis, manuscript preparation and review.

J.B Kwok contributed to data analysis, manuscript preparation and review.

G.M Halliday contributed to data analysis, manuscript preparation and review.

O. Piguet contributed to data analysis, manuscript preparation and review.

M.C Kiernan contributed to data analysis, manuscript preparation and review.

J.R Hodges contributed to study design, data collection, manuscript preparation and review.

Funding & Conflicts of Interest

This work was supported by funding to Forefront, a collaborative research group dedicated to the study of frontotemporal dementia and motor neurone disease, from the National Health and Medical research Council of Australia program grant (#1037746) and the Australian Research Council Centre of Excellence in Cognition and its Disorders Memory Node (#CE110001021). Dr Devenney is supported by the Motor Neurone Disease Association UK. Associate Professor Olivier Piguet is supported by an NHMRC Career Development Fellowship (APP1022684). Dr Michael Hornberger is supported by Alzheimers Research UK and the Isaac Newton Trust. We are grateful to the research participants involved with the ForeFront research studies.

The authors report no conflicts of interest.

References

1. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain : a journal of neurology. 2011 Sep;134(Pt 9):2456-77.

2. Chare L, Hodges JR, Leyton CE, et al. New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications. Journal of neurology, neurosurgery, and psychiatry. 2014 Aug;85(8):865-70.

3. Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? Journal of Neurology, Neurosurgery & Psychiatry. 2009;80(6):591-3.

4. Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. Neurology. 2008;71(19):1481-8.

5. Kipps CM, Hodges JR, Fryer TD, Nestor PJ. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. Brain : a journal of neurology. 2009:awp077.

6. Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. Neurology. 2010;74(20):1591-7.

7. Devenney E, Foxe D, Dobson-Stone C, Kwok JB, Kiernan MC, Hodges JR. Clinical heterogeneity of the C9orf72 genetic mutation in frontotemporal dementia. Neurocase. 2014(ahead-of-print):1-7.

8. Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. Journal of Neurology, Neurosurgery & Psychiatry. 2012;83(4):358-64.

9. Suhonen NM, Kaivorinne AL, Moilanen V, et al. Slowly progressive frontotemporal lobar degeneration caused by the C9ORF72 repeat expansion: a 20-year follow-up study. Neurocase. 2014(ahead-of-print):1-5.

10. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. Annals of neurology. 2004 Sep;56(3):399-406.

11. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. Annals of neurology. 2006;59(6):952-62.

12. Hornberger M, Piguet O. Episodic memory in frontotemporal dementia: a critical review. Brain : a journal of neurology. 2012;135(3):678-92.

13. Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. Dement Geriatr Cogn Disord. 2007;23(5):334-42.

14. Ambikairajah A, Devenney E, Flanagan E, et al. A visual MRI atrophy rating scale for the amyotrophic lateral sclerosis-frontotemporal dementia continuum. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014(0):1-9.

15. Wedderburn C, Wear H, Brown J, et al. The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. Journal of neurology, neurosurgery, and psychiatry. 2008 May;79(5):500-3.

16. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308-.

17. Goldman JS, Farmer JM, Wood EM, et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005 Dec 13;65(11):1817-9.

18. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry. 2006;21(11):1078-85.

19. Meyers J, Meyers K. The Meyers Scoring System for the Rey Complex Figure and the Recognition Trial: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1995.

20. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique.(Les problems.). Archives de psychologie. 1941.

21. Schmidt M. Rey auditory verbal learning test: a handbook: Western Psychological Services Los Angeles; 1996.

22. Wechsler D. Wechsler Memory Scale—Third Edition (WMS-III). . London: The Psychological Corporation.; 1998.

23. Burgess PW, Shallice T. Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia. 1996;34(4):263-72.

24. Spreen O, Strauss E. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary: Administration, Norms, and Commentary: Oxford University Press, USA; 1998.

25. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and motor skills. 1958;8(3):271-6.

26. Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, Hodges JR. Distinguishing Subtypes in Primary Progressive Aphasia: Application of the Sydney Language Battery. Dementia and Geriatric Cognitive Disorders. 2013;35(3-4):208-18.

27. McDonald S, Flanagan S, Rollins J, Kinch J. TASIT: A new clinical tool for assessing social perception after traumatic brain injury. The Journal of head trauma rehabilitation. 2003 May-Jun;18(3):219-38.

28. Young AW PD, Calder AJ, Sprengelmeyer R, Ekman P. Facial Expressions of Emotion - Stimuli and Tests (FEEST)

. Bury St Edmunds,England:: Thames Valley Test Company; 2002.

29. Dobson-Stone C, Hallupp M, Bartley L, et al. C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. Neurology. 2012;79(10):995-1001.

30. Renton AE, Majounie E, Waite A, et al. A Hexanucleotide Repeat Expansion in< i> C9ORF72</i> Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron. 2011;72(2):257-68.

31. Schofield EC, Halliday GM, Kwok J, Loy C, Double KL, Hodges JR. Low serum progranulin predicts the presence of mutations: a prospective study. Journal of Alzheimer's Disease. 2010;22(3):981-4.

32. Stanford PM, Shepherd CE, Halliday GM, et al. Mutations in the tau gene that cause an increase in three repeat tau and frontotemporal dementia. Brain : a journal of neurology. 2003;126(4):814-26.

33. Mackenzie IR, Rademakers R, Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. The Lancet Neurology. 2010 Oct;9(10):995-1007.

34. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer's & Dementia. 2012;8(1):1-13.

35. Tan RH, Pok K, Wong S, Brooks D, Halliday GM, Kril JJ. The pathogenesis of cingulate atrophy in behavioral variant frontotemporal dementia and Alzheimer's disease. Acta neuropathologica communications. 2013;1(1):30.

36. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000 Jun;11(6 Pt 1):805-21.

37. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics. 1982 Dec;38(4):963-74.

38. Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR. How preserved is episodic memory in behavioral variant frontotemporal dementia? Neurology. 2010;74(6):472-9.

39. Bertoux M, de Souza LC, Corlier F, et al. Two distinct amnesic profiles in behavioral variant frontotemporal dementia. Biological psychiatry. 2014 Apr 1;75(7):582-8.

40. Mahoney CJ, Beck J, Rohrer JD, et al. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. Brain : a journal of neurology. 2012 Mar;135(Pt 3):736-50.

41. Irish M, Devenney E, Wong S, et al. Neural substrates of episodic memory dysfunction in behavioural variant frontotemporal dementia with and without C9ORF72 expansions. NeuroImage Clinical. 2013;2:836-43.

42. Kumfor F, Irish M, Leyton C, et al. Tracking the progression of social cognition in neurodegenerative disorders. Journal of neurology, neurosurgery, and psychiatry. 2014 Oct;85(10):1076-83.

43. Happé F, Booth R, Charlton R, Hughes C. Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: Examining profiles across domains and ages. Brain and cognition. 2006;61(1):25-39.

44. Ashwin C, Chapman E, Colle L, Baron-Cohen S. Impaired recognition of negative basic emotions in autism: A test of the amygdala theory. Social neuroscience. 2006;1(3-4):349-63.

45. Irish M, Piguet O, Hodges JR, Hornberger M. Common and unique gray matter correlates of episodic memory dysfunction in frontotemporal dementia and alzheimer's disease. Human brain mapping. 2014;35(4):1422-35.

46. Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. Brain : a journal of neurology. 2011;134(9):2502-12.

47. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of neurology. 2004 Mar;55(3):306-19.

48. Dobson-Stone C, Luty AA, Thompson EM, et al. Frontotemporal dementia-amyotrophic lateral sclerosis syndrome locus on chromosome 16p12.1-q12.2: genetic, clinical and neuropathological analysis. Acta neuropathologica. 2013 Apr;125(4):523-33.

49. Devenney E, Hornberger M, Irish M, et al. Frontotemporal Dementia Associated With the C9ORF72 Mutation: A Unique Clinical Profile. JAMA neurology. 2014 Jan 20.

50. Byrne S, Heverin M, Elamin M, et al. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: A Population-

Based Case-Control Cohort Study of Familial and Sporadic Amyotrophic Lateral Sclerosis. Annals of neurology. 2013;9(10):23969.

Figure Legends

Figure 1: Flowcharts demonstrate the change in diagnosis over time for cases of probable bvFTD (Figure 1A) and possible bvFTD (Figure 1B) at presentation.

Figure 2: Behavioural features across the spectrum of bvFTD expressed as percentages of the total group. * $p < 0.05$

Figure 3: 3A demonstrates estimated marginal means based on the % change in ACE-R score across time for probable and possible bvFTD. Time ($p < 0.05$). Time x Diagnosis ($p < 0.05$). 3B demonstrates estimated marginal means based on the change in Functional Rating Scale (FRS) Rasch scores across time. Time ($p < 0.001$). Time x Diagnosis ($p < 0.001$). Error bars show 95% confidence intervals.

Figure 4: Results from voxel-based morphometry analyses demonstrating areas of grey matter density decrease for i) probable vs control (a-c - red), ii) possible vs control (d-f – yellow) and iii) probable vs possible (g-i – blue). Clusters are overlaid on the MNI standard brain (MNI152_T1_2mm_Brain). Coloured voxels show regions significant in the analyses for $p < 0.01$ corrected.

Figure 5: 5A demonstrates estimated marginal means based on the % change in ACE-R score across time for changers and non-changers. Time ($p < 0.05$). Time x Diagnosis ($p < 0.05$). 5B demonstrates estimated marginal means based on the change in Functional Rating Scale Rasch scores across time. Time ($p < 0.001$). Time x Diagnosis ($p < 0.001$). Error bars show 95% confidence intervals.

Figure 6: Results from voxel-based morphometry analyses demonstrating areas of grey matter density decrease for i) changers vs controls (a-c), ii) non-changers vs controls and iii) changers vs non-changers. Clusters are overlaid on the MNI standard brain (MNI152_T1_2mm_Brain). Coloured voxels show regions that were significant in the analyses for $p < 0.05$ corrected for between group comparisons and $p < 0.001$ uncorrected for between group comparisons.

Table 1. Demographics - Mean (standard deviation) scores for bvFTD patients vs. controls, probable vs. possible and changers vs. non-changers

Demographic data	**bvFTD**	**Controls**	***p* values**	**Probable**	**Possible**	**p values**	**Changers**	**Non-changers**	***p* values**
N	58	25	-	38	20	-	11	9	-
Sex (M:F)	46:12	14:11	n.s	28:10	18:2	n.s	9:2	9:0	n.s
Age at onset (years)	58.5 (7.9)	-	-	59.1 (8.2)	57.4 (4.2)	n.s	55.2 (8.2)	58.4 (8)	n.s
Education (years)	12 (3.1)	13.4 (2.3)	n.s	12.5 (3.2)	10.8 (2.7)	n.s	10.2 (1.7)	10.3 (2.8)	n.s
Disease Duration (years)	4.5 (3.0)	-	-	3.5 (2.4)	5.4 (3.6)	n.s	5.7 (3.6)	5 (3.5)	n.s
ACE-R (max 100)	76.1 (13.7)	94.5 (3.0)	***	72.4 (14.9)	83 (8)	*	80.3 (7.1)	86.1 (6.3)	**
FRS Rasch Score	-0.5 (1.4)	-	-	-0.7 (0.2)	0.2 (0.3)	**	.3 (1.2)	.3 (.7)	n.s

n.s. = non significant; *** = $p < 0.001$; ** = $p < 0.01$, *= $p < 0.05$

ACE-R = Addenbrookes Cognitive Examination – Revised

FRS = Functional Rating Scale

Table 2. Voxel-based morphometry results for entire bvFTD cohort vs. control corrected at $p < .05$, at a cluster threshold of greater than 50 contiguous voxels. No significant clusters for control vs. bvFTD.

Regions	***Hemisphere (L/R/B)***	***MNI coordinates for voxels of maximal intensity***			***No. of voxels***	***T value***
		X	**Y**	**Z**		
Cerebellum, insula, temporal lobe; hippocampus, opercular cortex, basal ganglia, thalamus, amygdala, heschl's gyrus, precuneus cortex, prefrontal cortex, anterior cingulate cortex, calcerine cortex, occipital pole, lateral occipital cortex, middle and inferior frontal gyri, angular gyrus, supramarginal gyrus, orbitofrontal cortex, frontal pole	B	42	-62	-58	101453	2
Precentral gyrus	R	16	-16	40	54	

Table 3: Neuropsychological test results in probable bvFTD, possible bvFTD and controls.

Domain	**Cognitive Test**	**Sub-test**	**Scores (Mean) SD**			***P* values**		
			Probable	**Possible**	**Controls**	**Prob vs. Poss**	**Prob vs Con**	**Poss vs Con**
General	ACE-R		72.4 (14.9)	83 (8)	94.5 (3.1)	**0.01**	< **0.001**	< **0.001**
Executive	TMT -Time difference		146.8 (98.9)	95.2 (62.4)	76.1 (32)	**0.05**	< **0.001**	< **0.001**
	Digit Span-Backwards		3.5 (1.4)	4.2 (1.2)	5.4 (1.2)	**0.05**	< **0.001**	< **0.001**
	Hayling	Cat A errors	7.2 (5)	2.4 (2.5)	.14 (.4)	< **0.001**	< **0.001**	< **0.001**
		Cat B errors	2.6 (2.4)	2.8 (2.2)	1 (1)	0.59	**0.01**	< **0.001**
	Letter Fluency		7.5 (3.7)	9.0 (5.3)	13.1 (3.2)	0.23	< **0.001**	< **0.001**
Memory	RAVLT	Immediate	4.8 (3.9)	7.3 (3.3)	9.6 (2.7)	**0.04**	**0.04**	**0.03**
		Delayed	4.6 (4)	6.3 (3.8)	10 (2.3)	0.15	< **0.001**	< **0.001**
	RCF: 3 min recall		6.6 (6.1)	12.6 (7.1)	18 (6)	**0.01**	< **0.001**	**0.02**
	Doors: Combined		5.9 (7.6)	12.3 (8.2)	19 (15)	**0.01**	< **0.001**	< **0.001**
Visuospatial	RCF: Copy score		28 (5.5)	25.8 (6.7)	32 (3.3)	0.23	< **0.001**	< **0.001**
Emotion	Ekman 60		33 (9.7)	40.3 (6.1)	49.3 (4.2)	**0.01**	< **0.001**	< **0.001**
	Tasit		13.5 (5.8)	18.9 (3.3)	24 (1.8)	< **0.001**	< **0.001**	< **0.001**
Language	Sydbat - Naming		19.9 (6.4)	23.1 (3.1)	27 (2)	0.18	< **0.001**	< **0.001**

Significant values at $p < 0.05$ indicated in bold.

ACE-R = Addenbrookes Cognitive Examination – Revised. TMT = Trail Making Task. RAVLT = Rey Auditory Verbal Learning Test. RCF = Rey-Osterrith Complex Figure. Sydbat = Sydney Language Battery. Prob =Probable, Poss=Possible, Con = Control

Table 4. Voxel-based morphometry results for probable vs. possible bvFTD, corrected at $p < .05$, at a cluster threshold of greater than 50 contiguous voxels. No significant clusters for possible vs. probable bvFTD.

Regions	***Hemisphere (L/R/B)***	***MNI coordinates for voxels of maximal intensity***			***No. of voxels***	***T value***
		X	**Y**	Z		
Probable vs. possible						**2**
Parahippocampal gyrus, hippocampus, amygdala, temporal fusiform cortex, planum polare, insula, superior, middle and inferior temporal gyrus, temporal pole, orbitofrontal gyrus, caudate, accumbens, caudate, frontal and central operculum cortex, heschls gyrus	R	28	-16	-24	5844	
Superior, inferior and middle temporal gyrus, hippocampus, parahippocampal gyrus, amygdala, insula, orbitofrontal cortex, caudate, putamen, temporal pole, frontal operculum cortex, subcallosal cortex	R	-56	-16	-10	5739	
Frontal pole, frontal medial cortex, paracingulate gyrus	B	10	56	-2	1798	
Inferior temporal gyrus	L	-58	-48	-28	176	

Table 5: Neuropsychological test results in changers, non-changers and controls

Domain	**Cognitive Test**	**Sub-test**	**Scores (Mean) SD**			***p* values**		
			Changers	**Non-Changers**	**Controls**	**Chg vs Non-Chg**	**Chg vs Con**	**Non-Chg vs Con**
General	ACE-R		78.4 (7.5)	87 (6.6)	94.5 (3.1)	**0.01**	**< 0.001**	**< 0.001**
Executive	TMT - Time difference		129.9(62.4)	108.7 (55.2)	76.1 (32)	**0.02**	**< 0.001**	0.1
	Digit Span Backwards		3.8 (0.9)	4.4 (1.5)	5.4 (1.2)	0.24	**< 0.001**	0.08
	Hayling	Cat A errors	4.7 (4.5)	1.3 (1.6)	.14 (.4)	**0.04**	**< 0.001**	**0.03**
		Cat B errors	2.9 (2.6)	2.4 (1.7)	1 (1)	0.8	**0.04**	**0.04**
	Letter Fluency		8.1 (4.4)	9.8(5.9)	13.1 (3.2)	0.9	**0.04**	**0.04**
Memory	RAVLT	Immediate	7 (2.7)	10 (4)	10 (2.3)	0.11	**0.04**	0.5
		Delayed	5.7 (3.6)	10.7 (3.4)	9.6 (2.7)	**0.03**	**0.04**	0.5
	RCF: 3 min recall		8.7 (5.7)	15.5 (6.7)	18 (6)	**0.02**	**< 0.001**	0.35
	Doors: Combined		6.9 (8.3)	16 (6.3)	19 (15)	**0.02**	**< 0.001**	0.07
Visuospatial	RCF: Copy score		25 (6)	27 (7)	32 (3.3)	0.36	**< 0.001**	**< 0.001**
Emotion	Ekman 60		39 (5.8)	41.5 (6.3)	49.3 (4.2)	0.2	**< 0.001**	**< 0.001**
	Tasit		19 (3.4)	18.6 (3.3)	24 (1.8)	0.8	**< 0.001**	**< 0.001**
Language	Naming		23 (2.7)	23.4 (3.5)	27 (2)	0.7	**< 0.001**	**0.03**

Significant values at $p < 0.05$ indicated in bold. ACE-R = Addenbrooke's Cognitive Examination – Revised. TMT = Trail Making Task. RAVLT = Rey Auditory Verbal Learning Test. RCF = Rey-Osterrith Complex Figure. Sydbat = Sydney Language Battery. Chg –changer. Non-chg –non-changer. Con = Control

Table 6. Voxel based morphometry results for changers vs controls and non-changers vs controls corrected at $p < .05$, and changers vs non-changers and non-changers vs changers uncorrected at $p < 0.01$, at a cluster threshold of greater than 50 contiguous voxels.

Regions	***Hemisphere (L/R/B)***	***MNI coordinates for voxels of maximal intensity***			***No. of voxels***	***T value***
		X	**Y**	**Z**		
Changers vs. controls						
Temporal pole, orbitofrontal cortex, insula, putamen	L	40	12	-6	663	2
Insula, opercular cortex, inferior frontal gyrus putamen	R	40	12	2	610	
Insula, opercular cortex	L	-30	10	8	200	
Occipital pole	L	-6	-90	14	117	
Occipital pole, orbitofrontal gyrus	L	-16	32	-22	63	
Middle and superior temporal gyrus	L	-50	-14	-14	53	
Inferior frontal gyrus	L	-56	22	2	51	
Non-changers vs. controls						
Frontal pole	R	20	66	14	222	2
Changers vs. Non-changers						
Insula, opercular cortex, putamen	R	26	18	-4	848	2
Thalamus	R	-16	-20	4	188	
Thalamus, hippocampus	L	10	-32	14	61	
Middle frontal gyrus	L	-30	24	34	61	
Middle frontal gyrus	L	-32	4	44	51	
Non-changers vs. changers						
Cerebellum	B	0	-48	14	135	2