HHS Public Access

Author manuscript

Neuroimage. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Neuroimage. 2019 April 01; 189: 645–654. doi:10.1016/j.neuroimage.2019.01.080.

The inner fluctuations of the brain in presymptomatic Frontotemporal Dementia: the chronnectome fingerprint.

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Abstract

Frontotemporal Dementia (FTD) is preceded by a long period of subtle brain changes, occurring in the absence of overt cognitive symptoms, that need to be still fully characterized. Dynamic network analysis based on resting-state magnetic resonance imaging (rs-fMRI) is a potentially powerful tool for the study of preclinical FTD.

In the present study, we employed a “chronnectome” approach (recurring, time-varying patterns of connectivity) to evaluate measures of dynamic connectivity in 472 at-risk FTD subjects from the Genetic Frontotemporal dementia research Initiative (GENFI) cohort.

We considered 249 subjects with FTD-related pathogenetic mutations and 223 mutation non-carriers (HC). Dynamic connectivity was evaluated using independent component analysis and sliding-time window correlation to rs-fMRI data, and meta-state measures of global brain flexibility were extracted.

Results show that presymptomatic FTD exhibits diminished dynamic fluidity, visiting less meta-states, shifting less often across them, and travelling through a narrowed meta-state distance, as compared to HC. Furthermore, global brain flexibility was significantly correlated to the expected age at symptom onset and processing speed performances in mutation carriers.

Dynamic connectivity changes characterize preclinical FTD, arguing for the desynchronization of the inner fluctuations of the brain. These changes antedate clinical symptoms, and might represent an early signature of FTD to be used as a biomarker in clinical trials.

Keywords

Frontotemporal Dementia; mutation; *Granulin*; *Microtuble Associate Protein Tau*; *C9orf72*; resting-state fMRI; dynamic brain functional connectivity; chronnectome

INTRODUCTION

Resting state functional magnetic resonance imaging (rs-fMRI) has become a useful tool to investigate the connectivity changes in neurodegenerative dementias[1, 2]. Spontaneous brain

activity at rest is organized in functionally specialized large-scale networks, that roughly correspond to different functional domains and that are selectively damaged by various neurodegenerative conditions[3].

However, previous results make the implicit assumption that the functional coupling among brain regions is static and unchanging over short periods of time[4–6].

This concept has since been modified with analytic approaches that capture the fact that the human brain is an interacting dynamic network and its architecture of coupling among brain regions varies across time (termed "the chronnectome")[7–12]. Dynamic connectivity studies have demonstrated reoccurring patterns of brain functional connectivity, or functional connectivity "states", that are reproducible over time and across subjects[8, 13, 14]. Initial dynamic connectivity studies were based on the assumption that subjects were allowed to be in only one "state" at a given point in time, while recent work has introduced the concept of "meta-states", suggesting that subjects may be in multiple states to varying degrees at the same point in time[7, 15]. Thus, for instance, if in the time-course we are able to identify six distinct states of functional dynamic connectivity, at a given point in time each subject will have a weighted probability to be in more than one state[15]. Meaningful measures of meta-state dynamic fluidity, such as the number of meta-states a subject passes through or the number of switches from one meta-state to another, have been suggested as an intuitive way to characterize global dynamic connectivity behaviour, showing promise for predicting mental states and cognitive performances[4, 16]. From this point of view, meta-state measures could provide a more "global" information on the effect of an ongoing neurodegenerative process, overcoming the evaluation of single specific brain areas or connectivity pathways, and evaluating global perturbation of the brain activity's temporal dynamics[7, 15].

Frontotemporal Dementia (FTD) is a neurodegenerative disease characterized by behavioural abnormalities, impairment of executive functions and language deficits[17, 18] and defined by focal frontotemporal atrophy[19]. In a significant proportion of the cases, FTD is an inherited autosomal dominant disorder; mutations in the *Granulin (GRN), chromosome 9 open reading frame 72* (*C9orf72)* or *Microtuble Associated Protein Tau (MAPT)* genes drive up to ~40% of Mendelian cases[20]. In genetic FTD, the neural substrates associated with the presymptomatic stage need to be fully characterized, even though the perturbation of static large-scale networks mainly involving the frontal regions has already been demonstrated[21, 22]. Namely, in presymptomatic genetic FTD increased connectivity in medial frontal regions[2, 23], especially within the Salience Network, and reduced seed-based connectivity between anterior cingulate cortex and posterior regions of the Default Mode Network[21] has been already reported. The evaluation of large-scale structural network topology along with their temporal dynamics might offer a theoretical framework that can contribute to understand the earliest abnormalities in FTD, with the new perspective of whole brain assessment[24].

These premises set the stage for the present study, in which we analyzed dynamic brain connectivity in presymptomatic subjects carrying *GRN, MAPT* or *C9orf72* mutations with the purpose *a)* to assess the chronnectome fingerprint by considering meta-state measures; *b*) to study the association between chronnectome changes and cognitive performances; and *c)*

to correlate chronnectome changes with expected age at disease onset, to evaluate if meta-state measures are associated with proximity to clinical onset. To this end, we analyzed rs-fMRI data of 472 subjects from the Genetic Frontotemporal Dementia Initiative (GENFI) cohort (http://genfi.org.uk) using a dynamic functional network connectivity (dFNC) approach to investigate the chronnectome in presymptomatic mutations carriers as compared to mutation non-carriers.

METHODS

Subjects.

Data for this study were drawn from the GENFI multicenter cohort study, which consists of 23 research centers in Europe and Canada. Inclusion and exclusion criteria have been previously described[25]. Local ethics committees approved the study at each site and all participants provided written informed consent according to the Declaration of Helsinki.

We considered asymptomatic participants at risk to carry *GRN, C9orf72* or *MAPT* mutations. Between January 2012 and January 2017, we considered 472 participants, of which 249 were mutation carriers (45 with *MAPT*, 122 with *GRN*, and 82 with *C9orf72* mutations) and 223 were mutation non-carriers. Subjects were enrolled from 18 centers belonging to the GENFI network (4 remaining centers were excluded from the present project for image artifacts, very low number of included subjects (<2), or for using 1.5T MRI scanner); the MRI parameters for each of the 18 included centers was reported in Supplementary Table 1. Demographic characteristics of mutation carriers and mutation non-carriers are reported in Table 1.

Estimated years from expected symptom onset in presymptomatic mutation carriers were calculated as the age of the participant at the time of the study assessment minus the mean familial age at symptom onset, as previously reported[25].

Included at-risk subjects underwent a careful recording of demographic data and a standardized clinical and neuropsychological assessment (derived from the Uniform Data Set[26]), as previously published[27]. We considered tests highly sensitive to identify initial changes in presymptomatic genetic FTD, as previously reported[25]. Thus, we considered assessment of behavioural symptoms with the Cambridge Behavioural Inventory Revised version (CBI-R)[28], general cognitive function with the Mini-Mental State Examination (MMSE)[26], and cognitive processing speed and executive functions assessed with the part A and part B of the Trial Making Test (TMT)[26], respectively. For each test, apart from the MMSE and CBI-R, we calculated Z scores based on language-specific norms[25]. Neuropsychological evaluation was harmonized across sites.

MRI acquisition.

MRI protocol was common to all the GENFI sites, and adapted for different scanners; no pre-study phantom harmonization was performed at local level. In summary, T2-weighted echo planar imaging (EPI) sequences sensitized to blood oxygenation level dependent (BOLD) contrast for rs-fMRI were considered in the present study (see Supplementary Table 1 for details on the fMRI protocol used by each site). As the repetition times (TRs, ranging

from 2200 ms to 2500 ms) and the volume numbers (ranging from 140 to 200) varied across the GENFI centres, we considered only the first 140 volumes of the EPI images for each subject (mean acquisition time: 311.5±4.95 sec). During scanning, subjects were asked to keep their eyes closed, not to think of anything in particular, and not to fall asleep.

Neuroimaging pre-processing and analysis.

Functional data were pre-processed using the toolbox for Data Processing & Analysis for Brain Imaging (DPABI, http://rfmri.org/dpabi)[29] based on the Statistical Parametric Mapping (SPM12) software.

For each subject, the first 2 volumes of the fMRI series were discharged to account for magnetization equilibration. The remaining 138 volumes underwent slice-timing correction and were realigned to the first volume. Any subject who had a maximum displacement in any direction larger than 2.5 mm, or a maximum rotation (x,y,z) larger than 2.5°, was excluded. Data were subsequently spatially normalized to the EPI unified segmentation template in Montreal Neurological Institute coordinates derived from SPM12 software and resampled to 3×3×3 cubic voxels. We preferred a normalization to the EPI template (instead of T1-based normalization) in line with recent data demonstrating that EPI normalization is able to reduce variability across subjects (especially when EPI distortion correction is not applied, as in our case) and boost the effective sample size by 15–25 %. Furthermore, studies assessing distance maps and intra subject variability in multicentre cohorts by EPI normalization are comparable with our data[30]. Spatial smoothing with an isotropic Gaussian kernel with full-width at half-maximum, 10 mm was applied; this threshold smoothing value was chosen for a number of reasons: 1) we assessed dFC within large areas, which are not usually affected by a relative large spatial smoothing; 2) we adopted in Abrol's template to estimate the dFC[31] (which has been calculated on 7500 healthy subjects) and consequently we opted for similar fMRI pipeline[32] (10 mm FWHM); 3) spatial smoothing of 8–10 mm FWHM is recommended to increase sensitivity[33].

Functional Networks Decomposition.

The functional imaging data were processed using the GIFT (GIFT toolbox, http://mialab.mrn.org/software/gift)[34] and a spatially constrained ICA algorithm[35] called Group Information Guided independent component analysis (GIG-ICA) was used to compute spatial maps that corresponded to those from a previous analysis[36]. In this approach, brain network spatial maps are used as reference templates to calculate functional networks for each individual subject one-by-one by maximizing independence in the context of the spatial constraint. These template maps include the brain networks with a neuronal origin (not artefactual) and assign the remaining data to be noise. We take advantage from the recently published set of 37 spatial maps derived from 7500 healthy subjects as spatial references for our network selection[31]. We then considered only cortical and subcortical networks, and we discharged cerebellar networks due to incomplete coverage of cerebellum in our sample, thus considering 35 spatial maps. The TR of each subject was entered in GIFT pre-processing, and we accounted for the differences in EPI acquisition protocols among centres. The Infomax approach was applied[37] to estimate the independent group components and 35 functional networks were considered (see Supplementary Figure 1 for details). Subject-

specific spatial patterns and time-courses were derived using spatial-temporal regression and then converted to Z-scores. The single time courses were detrended (to remove baseline drifts from the scanners and/or physiological pulsations), orthogonalized with respect to 12-motion parameters, despiked (replacement of outlier time points with 3rd order spline fitting to clean neighbouring points) and filtered using a 5th order Butterworth filter (0.01 to 0.15 Hz)[32].

Windowed functional network connectivity and correlation patterns decomposition (meta-states).

The dynamic functional network connectivity (dFNC) was achieved using dynamic FNC toolbox implemented in GIFT[38]. dFNC was assessed using a sliding-window approach to estimate correlation matrices between components for each segment. Segments were defined with a tapered window convolving a rectangle (width=30, TRs=66 sec) with a Gaussian (σ =3) and slide in steps of 1 TR. A LASSO approach with L1 regularization (100 repetitions) was used to compute the covariance between the independent component (IC) time-courses. To obtain the decomposition into connectivity patterns (CPs), the spatial ICA (sICA) approach was applied[14]. As previously described, the time-courses were discretized (to work over a more tractable space) into 8 bins (positive and negative quartiles) and each timepoint was ended into a meta-state[39]. The time-courses for sICA CPs were derived from the regression of each subject's dFNC information at each time window on the group of sICA CPs. During dFNC preprocessing the following covariates of no interest were considered: age, gender, acquisition site, scanner type, family number, genetic status of the proband, mean framewise displacement (calculated for each subject from the estimated motion parameters)[40] and the variance associated with them has been regressed out from the windowed dynamic functional network connectivity correlations for each subject at this processing step.

Four indexes of connectivity dynamism were considered: *i)* the number of distinct meta-states the subjects occupied during their scans (meta-state number); *ii)* the number of times that subjects switch from one meta-state to another (meta-state changes), *iii)* the largest distance of two meta-states that subjects occupied (meta-state span), and *iv)* the overall distance traveled by each subject through the state space (the sum of the L1 distances between successive meta-states, i.e. meta-state total distance).

Statistical analysis.

The assumption of normality for continuous variables was not satisfied for all group combinations, as assessed by Shapiro-Wilk's test ($p<0.05$). Thus, comparisons of demographic and clinical characteristics between groups (mutation carriers vs. mutation non-carriers) were assessed by Mann-Whitney U test for continuous variables and χ^2 test for categorical variables. Pearson's correlation was used to assess the relationship between the meta-state measures (meta-state number, meta-state changes, meta-state span and meta-state total distance) and age at expected symptom onset. Finally, partial correlation (considering age as a nuisance variable) was used to test the relationship between meta-state measures and cognitive/behavioural performances (CBI-R, MMSE, TMT-A, TMT-B). All the statistical analysis was performed using IBM SPSS Statistics 22.0 (Chicago, USA) and

statistical significance level set at $p< 0.05$, corrected for multiple comparisons (Benjamini-Hochberg False-Discovery-Rate (FDR) correction[41]), considering four meta-state measures and four clinical tests, either for direct comparisons (mutations carriers vs mutation non-carriers) and for correlation analyses (between age at expected symptom onset and meta-state measures and between clinical tests and meta-states measures). Finally, we considered each gene (*GRN, C9orf72* or *MAPT*) and we conducted exploratory analyses as preprocessing (Independent Component Analysis, ICA) was applied on all subjects together.

RESULTS

Two hundred-forty nine mutation carriers (82 with C9orf72, 122 with *GRN* and 45 with *MAPT* mutations) were considered, compared with 223 mutation non-carriers. Considering clinical and demographic variables, mutation non-carriers were slightly older (47.2±13.2 vs 44.7±11.7, p=0.042), in particular compared with *MAPT* mutation carriers (see Supplementary Table 2 for details). We considered six connectivity patterns (CPs) of dFNC, which are reported in Figure 1. The colors of each CP represent the direction and the strength of the correlation among the 35 considered network components (red: positive correlation and blue: negative correlation).

dFNC was expressed as a weighted sum of the discretized six-dimensional CPs, for each given point in time and for each subject. Mutation carriers exhibited diminished dynamic fluidity, as they occupied a fewer number of meta-states (i.e., meta-state numbers) and changed from one meta-state to another less often (i.e., meta-state changes) than mutation non-carriers (see Table 2). Furthermore, mutation carriers operated over a restricted dynamic range with decreased meta-state total distance, as they travelled less overall distance, between successive meta-states, through the state space than mutation non-carriers (see Table 2). We did not find any difference in meta-state span between groups.

In Figure 2, meta-state dynamics through time, meta-state numbers, meta-state change points, and meta-state total distance in a representative mutation carrier and in a representative mutation non-carrier were reported. A mutation non-carrier subject will show a greater brain dynamism as compared to a representative mutation carrier (**panel A**), as suggested by the more complex pattern in the former subject, with an higher number of realized meta-states (**panel B**), meta-state changes (**panel C**) also travelling a greater overall distance (**panel D**) compared to a mutation carrier subject.

In the exploratory analysis (not corrected for multiple comparisons), we evaluated *C9orf72*, *GRN* and *MAPT* mutation carriers separately, as compared to HC, *C9orf72* mutation carriers showed reduced meta-states numbers (p=0.032) and reduced meta-state changes (p=0.041), *MAPT* mutation carriers had reduced meta-states numbers (p=0.042) and reduced overall meta-state total distance (p=0.046), while we did not find significant findings in regard to *GRN* mutation carriers, as compared to HC.

The correlation between meta-state measures and age at expected onset in mutation carriers was then considered (FDR-corrected for multiple comparisons). The closer the age at expected symptom onset, the lower the number of meta-states (Pearson's correlation, r=

−0.174, p=0.012), the lower the meta-state changes (r=−0.166, p=0.012), the lower the meta-state span (r=−0.167, p=0.012) and the lower the meta-state total distance (r=−0.141, p=0.027) was found.

Finally, the correlation between meta-state measures and cognitive performance in mutation carriers and non-carriers, considering age at evaluation as a covariate, was assessed (not corrected for multiple comparisons). TMT-A scores (the higher the scores the worse the performances) were inversely correlated with meta-state span (r=−0.143, p=0.024) and meta-state total distance (r=−0.124, p=0.050): interestingly, exploring the correlation of TMT-A scores and meta-state measures, the inverse correlation with meta-state span was primarily related to *C9orf72* group (r=−0.281, p=0.011, not corrected for multiple comparisons). No other significant correlation between meta-state measures and neuropsychological/behavioural tests in the three mutation separately were demonstrated. No other significant correlations between meta-state measures and MMSE, CBI-R or TMT-B were found. No significant correlation between meta-state measures and neuropsychological/behavioural tests were evident.

DISCUSSION

In this study, results showed consistent evidence of reduced global flexibility and dynamism in the brain of presymptomatic FTD, which progressively worse with proximity to age at expected symptoms onset. Moreover, the impairment of global inner fluctuations of the brain was well correlated with processing speed performances in asymptomatic subjects carrying pathogenetic FTD mutations.

In the last decade, rs-fMRI has been used to estimate functional brain connectivity, considering regions with temporally coherent brain activity as “functional brain networks”[42, 43]. Up to now, most studies have relied on two implicit assumptions: the first is a “spatial assumption”, that each brain region participates in exactly one network, and the second is a “temporal assumption”, that the connectivity within each network are essentially static over time[14, 44–46]. New evidence clearly suggests that the brain is dynamically multistable, and spontaneous low-frequency fluctuations in BOLD fMRI data during the acquisition capture reoccurring patterns (states) of interactions among intrinsic networks at rest (chronnectome)[7, 47]. This is in line with spontaneous activity fluctuations found in electrophysiological studies[48–50]. Such findings open a new chapter in the study of neurodegenerative diseases, offering a different perspective to investigate the earliest brain changes, thus considering global brain connectivity instead of either single network connectivity or focal neural damage.

In the present study, we assessed the chronnectome fingerprint in preclinical monogenic FTD by considering meta-states. Meta-states properly describe whole brain flexibility, moving from the concept that each subject may be in a defined “state” of functional dynamic connectivity in at given point in time to the concept that a subject may have a weighted probability to be in more “states” in each given point in time. So, for each subject dynamic connectivity was represented by the sum of different connectivity pattern probability at the same time. From this point of view we explored indexes (meta-state numbers, changes, span,

total distance) that were related to the global dynamic properties of the brain rather than to a specific state behaviour. Figure 1 represented the six mean (considering all subjects) correlations' matrix that were considered simultaneously to define the dynamic connectivity parameters for each subject. On the other hand, Figure 2 showed the matrix of the six CPs through time for each subject: as you can see in the first row (A) a "visual" difference was present (mutation non-carrier appeared more dynamic than the mutation carrier) but the objective parameters (B, C, D: metastate number, changes, total distance travelled across metastates) were defined considering all the metastates in each point in time simultaneously. This core challenge allows us to better identify early and hidden features of brain disorders, as already demonstrated in schizophrenia[15].

Herein, we reported that asymptomatic mutation carriers a) passed through a lower number of distinct meta-states (i.e., lower meta-state number); b) less often switched between meta-states (i.e., lower meta-state changes), and c) switched frequently between two meta-states at close distal boundaries of the state space (i.e., lower mate-state total distance), as compared to mutation non-carriers. Altogether, these findings point to a precocious impairment of the inner fluctuations of the brain with an effect on *at-distance* networks through a diminished dynamic fluidity (meta-state number and meta-state changes) and a restricted dynamic range (meta-state total distance) in preclinical FTD[51].

Prior work has primarily focused on topological differences among networks in FTD, identifying structural and even functional changes of specific brain networks in preclinical disease[2, 21, 22, 25, 52–55] with specific neuropathological progression according with the molecular nexopathy paradigm[56]. In the present work, we suggested that FTD at the early stages also affects whole brain efficiency, providing a complementary and coordinated point of view on the presymptomatic phases of FTD.

Moreover, we reported that the greater the meta-state abnormalities in mutation carriers, the closer the age at expected onset, in line with the progressive changes which in turn lead to symptom onset and structural damage in FTD.

Finally, TMT-A, a test reflecting processing speed skills[57], inversely correlated with measures of dynamic range connectivity. This confirms and extends previous hypothesis of a strict link between chronnectome fingerprint and cognition performances[58, 59] that needs to be further explored, also considering the strength of correlations (low-moderate) in the mutation-carriers group . With regard to the discrepancy between cognitive (CBI-R) and behavioural (TMT-A in particular) association with meta-state measures it should be noted that the level of behavioural/cognitive symptoms in the preclinical phase of FTD is very low (not fulfilling diagnostic criteria for FTD), making behavioural and neuropsychological tests potentially useful only in the late preclinical phase of FTD (approximately 5 years before) as already demonstrated[25]. On the other hand, TMT-A, as index of preprocessing speed skill could represent a marker of the "global" brain perturbation in the preclinical phase of FTD, as captured by dynamic brain connectivity approach. Finally, no significant correlations between TMT-A and metastate measures in healthy controls were evident, supporting the idea that this findings in presymptomatic FTD were not primarily age-related.

Our study presents a number of limitations that need to be acknowledged. First, the influence of vigilance (considering that rs-fMRI data were collected eye-closed) was not evaluated[35]. Second, subject motion is of particular concern in dynamic analyses of rs-fMRI[60]. To overcome this limit, we included motion parameters estimation as well as mean framewise displacement in the preprocessing and in the statistical design, respectively[32, 40]. Third, considering the unconstrained nature of the resting-state signal, thought content during the scan represented a significant source of variability, can only be partially evaluated by retrospective questionnaires[13, 61]. Four , scan time of acquisition was in line with (or even greater than) previous studies[13, 14] even though the development of effective dynamic functional connectivity statistical approaches is still an open field, deserving attention in the future[15, 62–65].

Despite these limitations, to the best of our knowledge, this is the first study applying chronnectome approach to neurodegenerative dementias. The exploration of time-varying aspects of functional connectivity unveiled aspects of the underappreciated early brain changes in FTD and supported the view that at the very early disease stage FTD is affecting brain as global system, and only in a second phase the pathology involves selective focal regions. Therefore, FTD should be considered less focal than previously thought. These findings may have important implication on clinical grounds, as tracking desynchronization of the inner fluctuations of the brain might be a helpful prognostic marker to be used in future pharmacological and prevention trials and it could be considered a feasible approach to identify novel targets of intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank Dr. Paolo Semeraro for his valuable support in data preprocessing. This work was supported in part by grants from the NIH (R01REB020407, P20GM103472) as well as NSF grant 1539067.

APPENDIX

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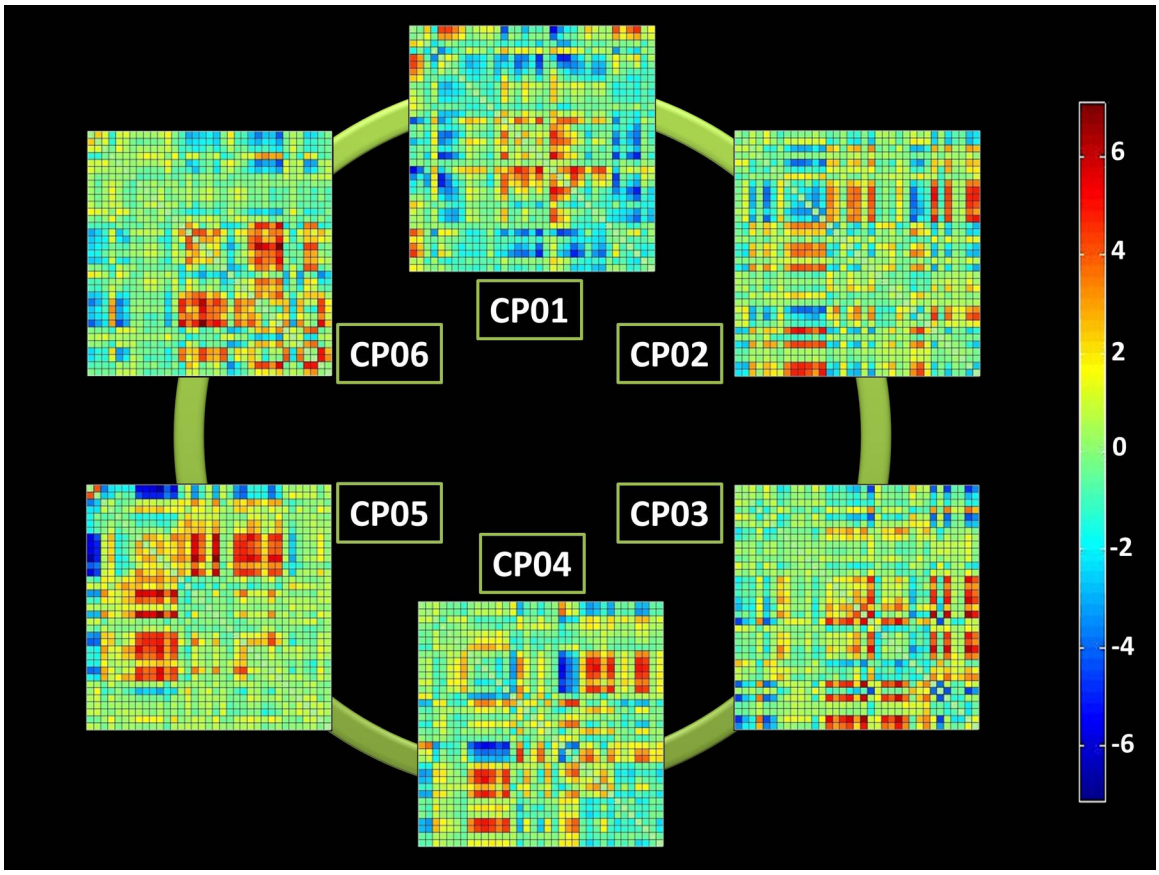

Figure 1. The six connectivity patterns (CPs) resulting from the dynamic Functional Network Connectivity (dFNC) analysis.

The six correlations' matrix (among the 35 considered network components) are reported. The colorbar represents the direction and the strength of each correlation (red: positive correlation, blue: negative correlation).

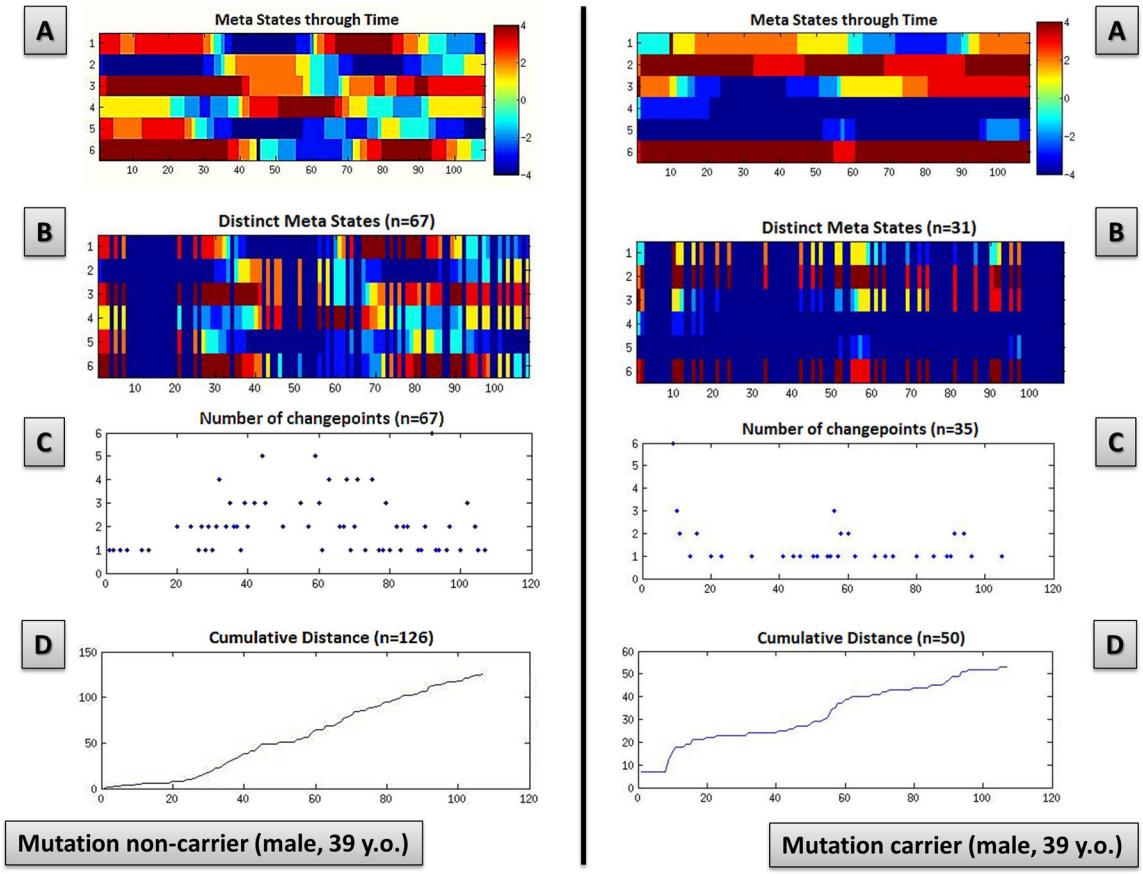

Figure 2. Meta-state dynamics through time, meta-state numbers, meta-state change points, and meta-state total distance in a representative mutation carrier and in a representative mutation non-carrier.

Meta-state dynamics through time (panel A), meta-state numbers (panel B), meta-state change points (panel C), and meta-state total distance (panel D) in a representative mutation non carrier (left column) and representative mutation carrier (right column).

The colorbar represents the strength of probability to be in each meta-state. X-axis: the six connectivity patterns (Cps) are reported, from 1 to 6; Y-axis: time (seconds, after timecourse discretization in quartiles).

Table 1.

Demographic characteristics of included participants.

Characteristic	Carriers (n=249)	Non-carriers (n=223)	P-value*
Age (years)	44.7±11.7	47.2±13.2	0.042
Female, %	64.7%	56.5%	0.073^
Education (years)	14.4±3.2	14.1±3.3	0.242
Years at expected onset (years)	−13.8±11.3	-	-
Cognitive and behavioural assessment			
MMSE	29.2±1.1	29.4±0.9	0.633
CBI-R	4.45±8.2	3.3±6.1	0.098
TMT-A (Z-scores)	−2.5±64.5	−10.2±70.3	0.075
TMT-B (Z-scores)	−8.2±80.7	−14.4±69.0	0.345

*Mann-Whitney U test, otherwise specified; ^Chi-Square test; results are expressed as mean±standard deviation, otherwise specified.MMSE: Mini-Mental State Examination; CBI-R: Cambridge Behavioural Inventory Revised version; TMT-A: part A of the Trial Making Test; TMT-B: part B of the Trial Making Test

Table 2.

Meta-state measures in the studied groups.

Variable	Carriers (n=249)	Non-carriers (n=223)	p*
Number of distinct metastates, mean±SD	51.0±8.9	53.1±8.8	0.024
Number of meta-state changes, mean±SD	51.3±8.5	53.3±8.1	0.024
Meta-state span, mean±SD	23.0±4.7	23.8±4.5	0.136
Meta-state total distance, mean±SD	82.1±17.5	86.2±17.3	0.027

*Mann-Whitney U test (carriers vs non-carriers) FDR-corrected for multiple comparisons; SD: standard deviation.