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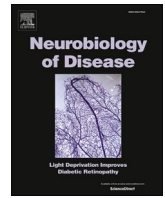
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## Early neurotransmitters changes in prodromal frontotemporal dementia: A GENFI study

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## ABSTRACT

**Background:** Neurotransmitters deficits in Frontotemporal Dementia (FTD) are still poorly understood. Better knowledge of neurotransmitters impairment, especially in prodromal disease stages, might tailor symptomatic treatment approaches.

**Methods:** In the present study, we applied JuSpace toolbox, which allowed for cross-modal correlation of Magnetic Resonance Imaging (MRI)-based measures with nuclear imaging derived estimates covering various neurotransmitter systems including dopaminergic, serotonergic, noradrenergic, GABAergic and glutamatergic neurotransmission.

We included 392 mutation carriers (157 *GRN*, 164 *C9orf72*, 71 *MAPT*), together with 276 non-carrier cognitively healthy controls (HC). We tested if the spatial patterns of grey matter volume (GMV) alterations in mutation carriers (relative to HC) are correlated with specific neurotransmitter systems in prodromal (CDR® plus NACC FTLD = 0.5) and in symptomatic (CDR® plus NACC FTLD ≥ 1) FTD.

**Results:** In prodromal stages of *C9orf72* disease, voxel-based brain changes were significantly associated with spatial distribution of dopamine and acetylcholine pathways; in prodromal *MAPT* disease with dopamine and serotonin pathways, while in prodromal *GRN* disease no significant findings were reported ( $p < 0.05$ , Family Wise Error corrected). In symptomatic FTD, a widespread involvement of dopamine, serotonin, glutamate and acetylcholine pathways across all genetic subtypes was found. Social cognition scores, loss of empathy and poor response to emotional cues were found to correlate with the strength of GMV colocalization of dopamine and serotonin pathways (all  $p < 0.01$ ).

**Conclusions:** This study, indirectly assessing neurotransmitter deficits in monogenic FTD, provides novel insight into disease mechanisms and might suggest potential therapeutic targets to counteract disease-related symptoms.

## 1. Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by progressive behavioral, linguistic, dysexecutive and motor disturbances (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). Its causes are genetic in about a third of cases, with mutations in *microtubule-associated protein tau* (*MAPT*), *progranulin* (*GRN*) and *chromosome 9 open reading frame 72* (*C9orf72*) being the commonest causes (Borroni and Padovani, 2013; Greaves and Rohrer, 2019). Behavioral variant FTD (bvFTD) is the most common presentation, followed by Primary Progressive Aphasia (PPAs) (Greaves and Rohrer, 2019). Symptomatic *MAPT* mutation carriers show a symmetrical brain atrophy involving mainly the anteromedial temporal lobes, symptomatic *GRN* mutation carriers exhibit a striking asymmetrical pattern of cortical atrophy, whereas symptomatic *C9orf72* mutation carriers display diffuse and symmetric cortical atrophy, involving also posterior regions, thalamus and cerebellum (Cash et al., 2018; Boeve et al., 2012; Whitwell et al., 2012). Early neuroimaging alterations are described around 5–10 years before phenoconversion with a specific distribution in each group (Rohrer et al., 2015).

Despite the continuous advancement of knowledge on disease-related mechanisms, little is known about neurotransmitter processes that occur in FTD. Exploring neurotransmitter pathways involved might shed more light on disease pathogenesis; moreover, since each mutation group is characterized by different clinical and imaging features, we might hypothesise that different neurotransmitter pathways are involved. As a consequence, research in this field might aid in identify tailored therapeutic targets for symptomatic interventions.

Although impairment of dopaminergic, serotonergic, GABAergic and glutamatergic pathways in autopsy studies has been demonstrated (Murley and Rowe, 2018), clinical trials have failed to report substantial benefits from neurotransmitter modulation on clinical symptoms in FTD (Panza et al., 2020). This discrepancy may be due to weaknesses in research methodology and small studies in unstratified populations.

Recent advancements in positron emission tomography (PET) and single photon computed emission tomography (SPECT) tracer development resulted in novel tracers that can reliably measure the availability of specific receptors. However, the need of large samples and of comparing multiple tracers in the same subjects have prevented reliable results on in vivo neurotransmitter pathways in neurodegenerative disorders, and especially in FTD. Indeed, only a few small series studies or case reports are available in FTD and in FTD-related mutations (Sperfeld et al., 1999; Miyoshi et al., 2010; Meloni et al., 2017; Carecchio et al., 2014; Leuzy et al., 2016; Takeshige et al., 2018; Murley et al., 2020).

To fill this gap, JuSpace toolbox has been recently developed with the aim to gather neurotransmitter pathways abnormalities combining MRI-based measures and a list of included PET and SPECT maps covering various neurotransmitter pathways (Dukart et al., 2018). JuSpace considers spatial pattern of brain alterations based on MRI measures derived by comparison between different groups (e.g. patients versus healthy controls), and it performs a correlation between these alterations and each receptor/transporter map included in the toolbox (Dukart et al., 2021). JuSpace therefore is able to explore if the spatial patterns of observed brain changes in the disease of interest are related to the distribution of specific neurotransmitters pathways, as derived

from independent healthy volunteer populations.

In the present study, we aimed to indirectly unravel neurotransmitter pathways changes, in particular in the earliest disease phases, namely in prodromal FTD, and to assess correlation with clinical symptoms. To achieve this, we applied JuSpace tool on a large sample of subjects from the international Genetic FTD Initiative (GENFI), considering individuals at different disease stages and with different pathogenetic mutations, and we evaluated impairment of dopamine, serotonin, glutamate, GABA, noradrenaline and acetylcholine systems.

## 2. Methods

### 2.1. Subjects

Data for this study were drawn from the GENFI multicenter cohort study, which consists of 26 research centers in Europe and Canada. Inclusion and exclusion criteria have been previously described (Rohrer et al., 2015). Local ethics committees approved the study at each site and all participants provided written informed consent according to the Declaration of Helsinki.

We considered both symptomatic patients fulfilling current clinical criteria for FTD (Rascovsky et al., 2011; Gorno-Tempini et al., 2011), and asymptomatic participants *at risk* to carry *GRN*, *C9orf72* or *MAPT* mutations. Between January 2012 and March 2020, we considered 668 participants, of which 392 were mutation carriers (157 with *C9orf72*, 164 with *GRN*, and 71 with *MAPT* mutations) and 276 were mutation non-carriers. Mutation carriers were grouped according to disease severity, as measured by Clinical Dementia Rating Dementia Staging Instrument plus behaviour and language domains from the National Alzheimer's Coordinating Center and Frontotemporal lobar degeneration modules (CDR® plus NACC FTLD, from here on referred as CDR) (Miyagawa et al., 2020) into asymptomatic subjects (CDR = 0), prodromal FTD (CDR = 0.5) or symptomatic FTD patients (CDR ≥ 1). Mutation non-carriers were considered as healthy control group (HC).

Included subjects underwent a careful recording of demographic data and a standardized clinical and neuropsychological assessment, as previously published (Premi et al., 2019).

### 2.2. MRI acquisition

MRI protocol was common to all the GENFI sites, and adapted for different scanners. Each subject underwent a 3 T MRI at each local site from three different manufacturers (Philips Healthcare- 215 subjects, GE Healthcare Life Sciences- 19 subjects, Siemens Healthcare Diagnostic- 434 subjects). The protocol included a volumetric T1-weighted MRI scan (magnetization-prepared rapid gradient echo, MPRAGE), as previously reported (Rohrer et al., 2015; Premi et al., 2017; Cash et al., 2018; Gazzina et al., 2019; Borrego-Écija et al., 2021). During scanning, subjects were asked to keep their eyes closed, not to think of anything in particular, and not to fall asleep.

### 2.3. MRI preprocessing and analyses

T1-weighted images were processed and analysed with the voxel-based morphometry (VBM) pipeline implemented in the Computational Anatomy Toolbox (CAT12 v.1742) ([www.neuro.uni-jena.de/cat](http://www.neuro.uni-jena.de/cat)) for SPM12 (SPM12 v.7219) ([www.fil.ion.ucl.ac.uk/spm/software/spm12](http://www.fil.ion.ucl.ac.uk/spm/software/spm12)) running on MATLAB R2019b (the MathWorks, Inc., Natick, Massachusetts, United States). The VBM pipeline consists of several stages (tissue segmentation, spatial normalization to a standard Montreal National Institute [MNI] template, modulation and smoothing), as previously described (Kurth et al., 2015). CAT12 potentially provides more robust and accurate performances compared to other VBM pipelines (Farokhian et al., 2017). The normalized and modulated grey matter images were then smoothed with 8 mm full width at half-maximum Gaussian kernel to reduce the probability of misalignment

errors, increasing the chance to detect differences over small regions of the brain.

To test for group differences in grey matter volume (GMV) a General Linear Model using SPM12 was implemented, considering age, gender and site as nuisance variables. The statistical threshold was set to  $p < 0.05$  corrected for multiple comparisons (whole-brain family-wise error, FWE).

### 2.4. Spatial correlation with neurotransmitter density maps

We used the JuSpace toolbox to test if the spatial patterns of GMV alterations in asymptomatic, prodromal and symptomatic FTD subjects (relative to HC) are correlated with specific neurotransmitter systems (Dukart et al., 2021). We considered a list of included PET and SPECT maps in JuSpace toolbox, covering various neurotransmitter systems (Dukart et al., 2021).

JuSpace creates a spatial pattern of GMV, comparing two different groups (e.g. patients versus healthy controls), and therefore aims to assess if the spatial patterns of brain changes observed in patients (as compared to healthy controls) are related to the distribution of specific neurotransmitters systems, these latter derived from independent healthy volunteer populations (Dukart et al., 2021). Thus, it performs a correlation between these alterations and each receptor/transporter map included in the toolbox.

Confounding effects of age, gender and site were regressed out from all images prior to these analyses (Dukart et al., 2021).

We considered serotonin transmission, i.e. the 5-hydroxytryptamine 1a (5-HT1a) receptor, the 5-HT1b receptor, the 5-HT2a receptor, and the serotonin transporter SERT; dopamine transmission, i.e. the D1 receptor, the D2 receptor, the dopamine transporter (DAT), and the FluoroDOPA, the GABA<sub>A</sub> receptors, the vesicular acetylcholine transporter (VACHT), the metabotropic glutamate receptor type 5 (mGLUR5), and the noradrenaline transporter (NAT). Each map included in Jspace toolbox was derived by PET data with the exception of DAT, which was derived from SPECT data, and each map was built up with specific numbers of healthy volunteers (Supplementary Table 1 for details). Using JuSpace toolbox, native normalized, modulated and smoothed grey matter images were parceled in regions of interest using the Neuromorphometrics Atlas (MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling, [www.masi.vuse.vanderbilt.edu/workshop2012/index.php/Challenge\\_Details](http://www.masi.vuse.vanderbilt.edu/workshop2012/index.php/Challenge_Details)). Mean regional values of GMV were extracted for all patients and HC. Spearman correlation coefficients (Fisher's Z transformed) were calculated between these z-transformed GMV maps of the patients and the spatial distribution of the respective neurotransmitter maps included in JuSpace toolbox. Exact permutation-based p-values as included in JuSpace (10,000 permutations randomly assigning group labels using orthogonal permutations) were computed to check if the distribution of the observed Fisher's z-transformed individual correlation coefficients were significantly different from zero. All analyses were Family Wise Error (FWE) corrected for the number of tests. Spearman correlation coefficients (Fisher's Z transformed) were calculated between these z-transformed GMV maps and the spatial distribution of the respective neurotransmitter maps. Exact permutation-based p-values as implemented in JuSpace (10,000 permutations randomly assigning group labels using orthogonal permutations) were computed to test if the observed correlation coefficients across patients deviate from a null distribution.

### 2.5. Statistical analysis

Comparisons of demographic and clinical characteristics were performed by the Student's *t*-test for continuous variables and the  $\chi^2$  test for categorical variables.

Spearman correlation was used to assess the relationship between each neurotransmitter output obtained with Jspace (i.e., the GMV-neurotransmitters correlation, Fisher's Z transformed) and clinical or



behavioral data. Statistical significance was set at  $p < 0.05$ , corrected for multiple comparisons (Family Wise Error-FWE) (SPSS Statistics 22.0, Chicago, USA).

### 3. Results

#### 3.1. Participants

Demographic characteristics of mutation carriers and non-carriers are reported in Table 1. In the present study, we considered 157 *C9orf72* expansion carriers, namely 85 asymptomatic, 33 prodromal and 39 symptomatic subjects; 164 with *GRN* mutation carriers, namely 107 asymptomatic, 33 prodromal and 24 symptomatic subjects, and 71 *MAPT* mutation carriers, namely 39 asymptomatic, 18 prodromal and 14 symptomatic subjects.

Standard voxel-wise analyses of GMV demonstrated the typical pattern of brain atrophy in mutations subgroups, according to disease stage, as previously published (Rohrer et al., 2015; Cash et al., 2018; Beck et al., 2008; Boeve et al., 2012; Josephs et al., 2009; Mahoney et al., 2012; Sha et al., 2012; Whitwell et al., 2012) (see Supplementary Fig. 1).

#### 3.2. Neurotransmitters deficits in *C9orf72* expansion carriers

In prodromal stage of *C9orf72* disease ( $CDR = 0.5$ ), as compared to HC, voxel-based brain changes were significantly associated with spatial distribution of dopamine transporter DAT ( $r = -0.13$ ,  $p = 0.02$ ) and acetylcholine transporter ( $r = -0.12$ ,  $p = 0.02$ ). In fully symptomatic stage ( $CDR \geq 1$ ), additional voxel-based brain changes were significantly associated with spatial distribution of.

5-HT1a receptors ( $r = -0.30$ ,  $p = 0.01$ ), D1 receptors ( $r = -0.28$ ,  $p = 0.01$ ), FDOPA ( $r = -0.13$ ,  $p = 0.02$ ), and mGluR5 ( $r = -0.20$ ,  $p = 0.01$ ) (see Fig. 1 and Table 2). The negative correlation coefficients indicate GMV reduction in patients as compared to HC in areas with high neurotransmitters density.

There was no significant difference in spatial distribution in asymptomatic expansion carriers ( $CDR = 0$ ) as compared to HC.

#### 3.3. Neurotransmitters deficits in *GRN* mutation carriers

No voxel-based brain changes were significantly associated with neurotransmitter spatial distribution in prodromal *GRN* disease ( $CDR = 0.5$ ). In fully symptomatic stage ( $CDR \geq 1$ ), as compared to HC, voxel-based brain changes were significantly associated with spatial distribution of 5-HT1a receptors ( $r = -0.25$ ,  $p = 0.01$ ), D1 receptors ( $r = -0.24$ ,  $p = 0.01$ ), dopamine transporter DAT ( $r = -0.14$ ,  $p = 0.01$ ), FDOPA ( $r = -0.11$ ,  $p = 0.02$ ), acetylcholine transporter ( $r = -0.16$ ,  $p = 0.02$ ), and mGluR5 ( $r = -0.23$ ,  $p = 0.01$ ) (see Fig. 1 and Table 2).

There was no significant difference in spatial distribution in asymptomatic mutation carriers ( $CDR = 0$ ) as compared to HC.

**Table 1**  
Demographic and clinical characteristics of the studied group.

Variable	HC	<i>C9orf72</i>	<i>GRN</i>	<i>MAPT</i>	p-value*
Number	276	157	164	71	
Age, years	46.5 ±	49.6 ±	48.5 ±	44.6 ±	
	13.2	13.2	12.9	12.8	0.02
Sex, female %	57.6	54.1	59.8	52.1	0.14 <sup>^</sup>
Education, years	14.3 ±	14.0 ± 3.2	14.2 ±	14.6 ±	
	3.3		3.8	3.0	0.56

Demographic characteristics are expressed as mean ± standard deviation, unless otherwise specified. HC = Healthy controls, *C9orf72* = chromosome 9 open reading frame 72 mutation carriers; *GRN* = progranulin mutation carriers; *MAPT* = microtubule-associated protein tau mutation carriers; \*Student-t-test, unless otherwise specified; <sup>^</sup> Chi-Square test.

#### 3.4. Neurotransmitters deficits in *MAPT* mutation carriers

In prodromal stage of *MAPT* disease ( $CDR = 0.5$ ), as compared to HC, voxel-based brain changes were significantly associated with spatial distribution of 5-HT1a receptors ( $r = -0.34$ ,  $p = 0.01$ ), D1 receptors ( $r = -0.20$ ,  $p = 0.01$ ), dopamine transporter DAT ( $r = -0.30$ ,  $p = 0.01$ ), FDOPA ( $r = -0.16$ ,  $p = 0.01$ ), and SERT ( $r = -0.16$ ,  $p = 0.01$ ). In fully symptomatic stage ( $CDR \geq 1$ ), additional voxel-based brain changes were significantly associated with spatial distribution of 5-HT1b receptors ( $r = 0.14$ ,  $p = 0.02$ ) and acetylcholine transporter ( $r = -0.18$ ,  $p = 0.02$ ) (see Fig. 1 and Table 2).

There was no significant difference in spatial distribution in asymptomatic mutation carriers ( $CDR = 0$ ) as compared to HC.

#### 3.5. Neurotransmitter impairment and social cognition in monogenic FTD

We assessed the relationship between GMV-neurotransmitters correlation coefficients and social cognition/loss of empathy data in monogenic FTD patients ( $CDR > 0$ ). We considered only GMV-neurotransmitters correlation coefficients significantly impaired in FTD and we excluded those highly correlated to each other (Spearman correlations coefficients > 0.80), namely FDOPA. Thus, we included in the present analyses 5-HT1a receptors, D1 receptors, DAT, VAChT, and mGluR5.

We considered a) Ekman facial emotion recognition task and *Faux-pas* recognition test (mini-SEA) scores (the lower the scores the worse the performances) (Funkiewiez et al., 2012), and b) loss of empathy and c) poor response to social/emotional cues, as reported by caregiver (which were rated on a 5-point scale: 0 = absent, 0.5 = questionable/very mild, 1 = mild, 2 = moderate, and 3 = severe). Significant threshold was set at  $p \leq 0.002$ , after correction for multiple comparisons.

In *C9orf72* expansion carriers, mini-SEA scores ( $n = 58$ ) were positively correlated with the strength of GMV colocalization of 5HT1a receptors ( $r = 0.449$ ,  $p < 0.001$ ) and D1 receptors ( $r = 0.402$ ,  $p = 0.002$ ); loss of empathy ( $n = 71$ ) was negatively correlated with D1 receptors ( $r = -0.423$ ,  $p < 0.001$ ) and poor response to emotional cues ( $n = 71$ ) with 5HT1a receptors ( $r = -0.406$ ,  $p < 0.001$ ) and D1 receptors ( $r = -0.454$ ,  $p < 0.001$ ). No other significant correlations between cognitive data and GMV neurotransmitters co-localization at pre-established statistical threshold were reported.

In *GRN* mutation carriers, loss of empathy ( $n = 57$ ) was negatively correlated with D1 receptors ( $r = -0.439$ ,  $p = 0.001$ ) and poor response to emotional cues ( $n = 57$ ) with D1 receptors ( $r = -0.542$ ,  $p < 0.001$ ) and DAT ( $r = -0.497$ ,  $p < 0.001$ ).

The relatively low number of prodromal or symptomatic *MAPT* mutation carriers prevented us to run correlation analyses in this group.

### 4. Discussion

In the last years, a giant step forward has been made in the knowledge of genetic basis of FTD and gene-related pathogenetic mechanisms, and more recently experimental therapeutic trials targeting *C9orf72*, *GRN*, or *MAPT* have been proposed.

Despite this, neurotransmitter impairment in monogenic FTD and differences according to causative gene have not been assessed yet. Restoring these deficits, individually or in combination, has the potential advantage to improve clinical and behavioral symptoms and may help in further understanding of the disease.

In the present work, we investigated if the spatial distribution of grey matter atrophy observed in different subtypes of monogenic prodromal and symptomatic FTD are related to the localization of specific neurotransmitters pathways as derived from independent healthy volunteer populations (Dukart et al., 2021). These data have been obtained by JuSpace toolbox, which compares PET and SPECT derived neurotransmitter maps with other imaging modalities such as MRI data (Dukart

Mutation	C9orf72		GRN		MAPT	
	0.5	≥1	0.5	≥1	0.5	≥1
CDR plus NACC FTLD						
5HT1a						
5HT1b						
5HT2a						
SERT						
D1						
D2						
DAT						
FDOPA						
GABA -A						
NAT						
VAcHT						
mGLUR5						

**Fig. 1.** Results of spatial correlation analyses according to mutation and disease stage.

Significant correlations for each neurotransmitter map in the different genetic groups are represented, considering each mutation group (*C9orf72*, *GRN*, *MAPT*) and disease stage according to Clinical Dementia Rating Dementia Staging Instrument plus behaviour and language domains from the National Alzheimer's Coordinating Center and Frontotemporal lobar degeneration modules (CDR plus NACC FTLD, here referred as CDR).

5HT = 5-hydroxytryptamine; SERT = serotonin transporter; D = dopamine; DAT = dopamine transporter; FDOPA = Fluorodopa; GABA<sub>A</sub> =  $\gamma$ -Aminobutyric acid type A; NAT = noradrenaline; VAcHT = Vesicular acetylcholine transporter; mGLUR5 = metabotropic glutamate receptor type 5.

*p*-values < 0.01 in blue and *p*-values < 0.05 in red, corrected for multiple comparisons (Bonferroni's correction). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2021). In our study, we considered grey matter atrophy as an imaging marker of neurodegeneration; however, other biomarkers might be even more sensitive, in particular in the prodromal phase (e.g. measures derived from functional imaging data).

We reported that grey matter alterations in the prodromal disease stages specifically co-localised with different neurotransmitters pathways, involving dopamine and cholinergic systems in *C9orf72* expansion carriers, dopamine and serotonin in *MAPT* mutation carriers, and with no significant detectable changes in *GRN* mutation carriers. Indeed, it has been reported that TDP-43 proteinopathy, the pathological hallmark of *C9orf72* expansions, may cause dopamine alterations (Funkiewiez et al., 2012) and that *C9orf72* expansion carriers exhibit more pronounced memory deficits as compared to *MAPT* and *GRN* mutation carriers (Funkiewiez et al., 2012), tasks for which cholinergic system is key. On the other hand, in regard to *MAPT* mutations, it has been proposed a link between dopamine and serotonin neurotransmission and phosphorylation state of tau protein (Koppel et al., 2019; Ramos-Rodriguez et al., 2013), with tau being able to disrupt the survival of dopaminergic and serotonergic neurons in *Drosophila* and in animal models (Wu et al., 2013; Khan et al., 2022). Finally, the lack of significant findings in *GRN* mutation carriers is in line with previous imaging studies reporting less functional and structural brain abnormalities in the prodromal stages than other genetic subtypes (Cash et al., 2018; Borroni et al., 2012; Premi et al., 2016; Premi et al., 2021).

Conversely, symptomatic disease was associated with a broad involvement of different circuits and significant changes of dopaminergic, serotonergic and cholinergic pathways in all monogenic FTD subtypes. We also found additional glutamatergic pathway involvement in *C9orf72* and *GRN* symptomatic mutations carriers. Of note, GABAergic and noradrenergic pathways resulted spared in monogenic FTD. These findings confirm and extend previous literature data on autopsy studies as well as a recent study on a large group of PPA patients (Premi et al., 2022), but also suggest an additional involvement of cholinergic system in monogenic FTD which is absent in sporadic disease (Murley and Rowe, 2018; Benussi et al., 2019). As compared to previous studies (Murley and Rowe, 2018), we indeed failed to confirm a co-localization of grey matter alteration and the GABAergic system.

Interestingly, we also suggest that dopamine and serotonin pathways may be associated with social cognition deficits and loss of empathy, which represents an early clinical feature in FTD (Toller et al., 2023). Dopamine, in addition to be linked to movement disorders, has long been known for its role in reward processing and emotional recognition (Fernandez et al., 2017; Schuster et al., 2022), and most recently a central role of serotonin circuits has been recognized in emotion

regulation and social behaviour (Canli and Lesch, 2007; Kanen et al., 2021; Duerler et al., 2022).

Most studies evaluating pharmacological approaches in FTD have not reported clear-cut results (Panza et al., 2020). Findings herein reported argue for further considering pharmacological manipulation of specific neurotransmitters, specifically considering FTD subtypes and disease stage to counteract related symptoms. In this view, investigating neurotransmitter pathways involved might aid in identifying biochemical alterations, which together with clinical, biological and neuroimaging biomarkers might be helpful to characterize more in detail the different FTD subtypes. In comparison to other biomarkers, exploring neurotransmitter impairment might hold the advantage to identify tailored therapeutic targets to improve symptomatic treatment.

Nonetheless, we acknowledge that this study entails some limitations. First, future implemented neurotransmitters maps in JuSpace may further refine the present findings. Moreover, the maps available have been recently obtained, and present some limitations that might be addressed, e.g. the variability in the number of controls cases in each map and receptor density assessment is not necessarily related to neurotransmitter density. Moreover, JuSpace toolbox has not yet been validated in aging populations with substantial atrophy. Second, we considered prodromal monogenic FTD, and these results cannot be extended to prodromal sporadic disease. Third, other toolbox mapping neurotransmitter systems and their implementation, such as NeuroMaps, may be also considered (Markello et al., 2022). Finally, JuSpace toolbox indirectly assess neurotransmitter impairment, and post mortem studies are warranted to confirm the results herein observed.

In conclusions, this study suggests that JuSpace is a helpful tool to indirectly assess neurotransmitter deficits in neurodegenerative dementias and may provide novel insight into disease mechanisms and intervention pharmacological targets.

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**Table 2**

Results of spatial correlation analyses for included participants according to mutation subtype and disease stage.

Mutation	CDR = 0.5		CDR ≥ 1	
	<i>r</i>	<i>p</i> -value	<i>r</i>	<i>p</i> -value
<b>C9orf72</b>				
5HT1a	-0.08	0.38	<b>-0.30</b>	<b>0.01</b>
5HT1b	0.01	0.98	-0.01	0.91
5HT2a	-0.01	0.98	-0.09	0.26
SERT	-0.09	0.08	-0.08	0.91
D1	-0.01	0.09	<b>-0.28</b>	<b>0.01</b>
D2	-0.08	0.26	0.02	0.91
DAT	<b>-0.13</b>	<b>0.02</b>	<b>-0.22</b>	<b>0.01</b>
FDOPA	-0.05	0.64	<b>-0.13</b>	<b>0.02</b>
GABAa	0.07	0.98	-0.07	0.91
NAT	-0.08	0.16	0.04	0.55
VAcHT	<b>-0.12</b>	<b>0.02</b>	<b>-0.20</b>	<b>0.01</b>
mGluR5	-0.07	0.45	<b>-0.20</b>	<b>0.01</b>
<b>GRN</b>				
5HT1a	-0.05	0.94	<b>-0.25</b>	<b>0.01</b>
5HT1b	-0.03	0.94	-0.02	0.73
5HT2a	-0.04	0.94	-0.08	0.14
SERT	0.02	0.94	-0.02	0.73
D1	-0.06	0.94	<b>-0.24</b>	<b>0.01</b>
D2	0.02	0.94	0.01	0.73
DAT	-0.03	0.94	<b>-0.14</b>	<b>0.01</b>
FDOPA	-0.02	0.94	<b>-0.11</b>	<b>0.02</b>
GABAa	-0.01	0.94	-0.01	0.73
NAT	0.01	0.94	0.06	0.22
VAcHT	-0.08	0.44	<b>-0.16</b>	<b>0.01</b>
mGluR5	-0.09	0.36	<b>-0.23</b>	<b>0.01</b>
<b>MAPT</b>				
5HT1a	<b>-0.34</b>	<b>0.01</b>	<b>-0.50</b>	<b>0.01</b>
5HT1b	0.09	0.30	<b>0.14</b>	<b>0.02</b>
5HT2a	-0.01	0.97	0.02	0.73
SERT	<b>-0.16</b>	<b>0.01</b>	<b>-0.26</b>	<b>0.01</b>
D1	<b>-0.20</b>	<b>0.01</b>	<b>-0.37</b>	<b>0.01</b>
D2	0.04	0.97	0.13	0.07
DAT	<b>-0.30</b>	<b>0.01</b>	<b>-0.45</b>	<b>0.01</b>
FDOPA	<b>-0.16</b>	<b>0.01</b>	<b>-0.36</b>	<b>0.01</b>
GABAa	-0.01	0.97	0.06	0.73
NAT	0.01	0.97	0.11	0.08
VAcHT	-0.12	0.14	<b>-0.18</b>	<b>0.02</b>
mGluR5	-0.05	0.97	-0.05	0.73

Fisher's *z*-transformed correlation coefficients (*r*) for each neurotransmitter map are reported, with corresponding *p*-values. The negative correlation coefficients indicate GMV reduction in patients as compared to HC in areas with high neurotransmitters density.

Significant results in boldface; *p*-values corrected for multiple comparison (FWE correction).

CDR = Clinical Dementia Rating Dementia Staging Instrument plus behaviour and language domains from the National Alzheimer's Coordinating Center and Frontotemporal lobar degeneration; 5HT = 5-hydroxytryptamine; SERT = serotonin transporter; D = dopamine; DAT = dopamine transporter; FDOPA = Fluorodopa; GABAa =  $\gamma$ -Aminobutyric acid type A; NAT = noradrenaline; VAcHT = Vesicular acetylcholine transporter; mGLUR5 = metabotropic glutamate receptor type 5.

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The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors. EP and MP planned the study, carried out statistical analysis, contributed to interpretation of the results and drafted the initial version of the manuscript; IM carried out statistical analysis and contributed to interpretation of the results; JD contributed to interpretation of the results. VC, RG, EB, AP, MB, EGT, AB, DMC, RSC, LLR, PF, DLT, JvS, LCJ, HS, DG, RS-V, RL, FM, MS, CG, MM, MCT, JBR, KAT, RV, EF, PT, AdeM, IS, CRB, SD, AG, JL, MO, SS, ILB, FP and JDR contributed to the conception of GENFI and acquisition of data and revised the manuscript for content. BB planned the study, carried out statistical analysis, contributed to interpretation of the results and drafted the initial version of the manuscript.

## Data availability

All study data, including raw and analysed data, and materials will be available from the GENFI Coordinator upon reasonable request. The software applied is publicly available at <https://github.com/juryxy/JuSpace>.

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## Appendix B. Supplementary data

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