Resting-state alterations in behavioral variant frontotemporal dementia are related to the distribution of monoamine and GABA neurotransmitter systems

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Introduction

- **Behavioral variant frontotemporal dementia** (bvFTD) [1,2]
  - detrimental changes in personality and behavior
  - short survival
  - rapid cognitive and functional decline
- Patients are **often** (i.e. up to 50%) **misdiagnosed** as having a psychiatric illness [3]
  → consideration of family history and different neuroimaging modalities necessary (e.g. FDG-PET, MRI) [1,4]
- **Structural alterations** (atrophy) in later stages **and functional alterations** (glucose hypometabolism) in earlier stages visible [5,6]
  → accompanied by **changes on neurotransmitter level**
- Neurotransmitter alterations in **frontotemporal dementia** (FTD): deficits in dopaminergic, serotonergic, cholinergic, glutamatergic, and GABAergic neurotransmitter systems [7,8]
- Neurotransmitter alterations might be **related to symptoms** (e.g. GABAergic deficit and disinhibition) [9,10]

Aim: examine the role of several neurotransmitter systems in the pathology of bvFTD

Methods

Sample *1
- **52 bvFTD patients** (mean age = 61.5 ± 10.0 years; 14 female)
- **22 healthy controls** (HC; mean age = 63.6 ± 11.9 years; 13 female)

→ resting-state fMRI and neuropsychological test data *2

Preprocessing (SPM12)
- Realigned & unwarped
- Co-registered to the structural image
- Spatially normalized to MNI space
- Smoothed by a Gaussian convolution kernel with 6 mm full-width at half maximum

Grey matter mask

First-level analysis
- REST toolbox version 1.8 [13]
  → regressed out first principal components for WM & CSF signals and 24 motion parameters

fractional **A**mplitude of **L**ow **F**requency **F**luctuations (fALFF)

$$= \frac{\text{power within low-frequency range } (0.01 - 0.08 \text{ Hz})}{\text{total power}}$$

Second-level analysis
- **SPM12**: **flexible factorial design** with group (patient/HC) as factor and age and gender as covariates
- **JuSpace toolbox** [14]: spatial correlation of fMRI data with neurotransmitter maps *3
  → correlation with neuropsychological test data
- **MENGA toolbox** [15]: spatial correlation with mRNA gene expression profile maps

→ age and gender corrected

Grey Matter Density (GMD) / atrophy → Functional alterations driven by structural changes?

*1 German FTLD consortium [11] & Max-Planck-Institute Leipzig database [12]
*2 Mini-Mental State Exam (MMSE), Verbal Fluency, (VF) (animals), Boston Naming Test (BNT), Trail Making Test B (TMT-B), Apathy Evaluation Scale (AES) (clinician-rated), Frontal Systems Behavior Scale (FrSBe), and Clinical Dementia Rating-FTLD scale-modified (CDR-FTLD)
*3 serotonin 1a (5HT1a) receptor, serotonin 1b (5HT1b) receptor, serotonin 2a (5HT2a) receptor, dopamine D1 receptor, dopamine D2 receptor, dopamine transporter (DAT), Fluorodopa (FDOPA), γ-Aminobutyric acid type A (GABAa) receptors, μ-opioid (MU) receptors, noradrenaline transporter (NAT), and serotonin transporter (SERT)

Results

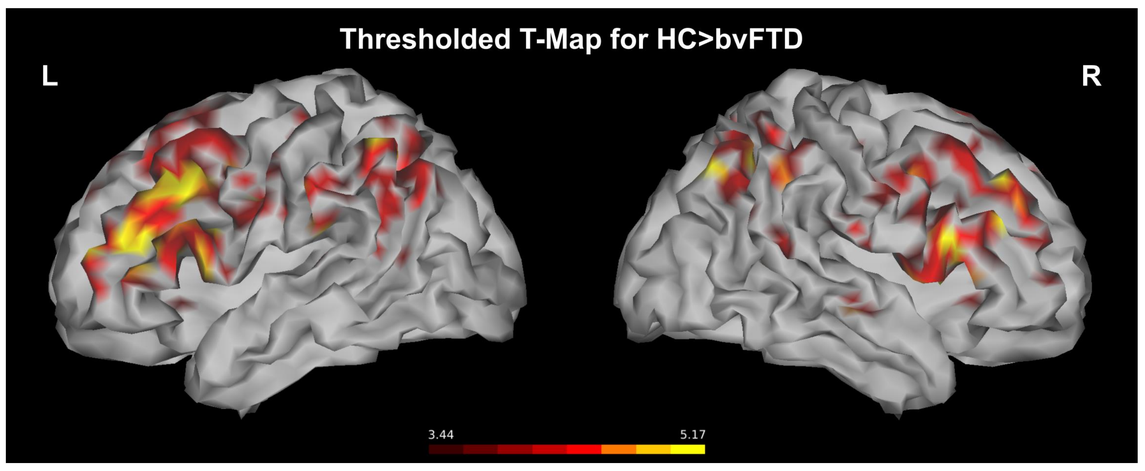


Figure 1. Thresholded fALFF t-map for HC>bvFTD. *Permutation-based threshold at cluster-level p<.05 and voxel-level p<.001.*

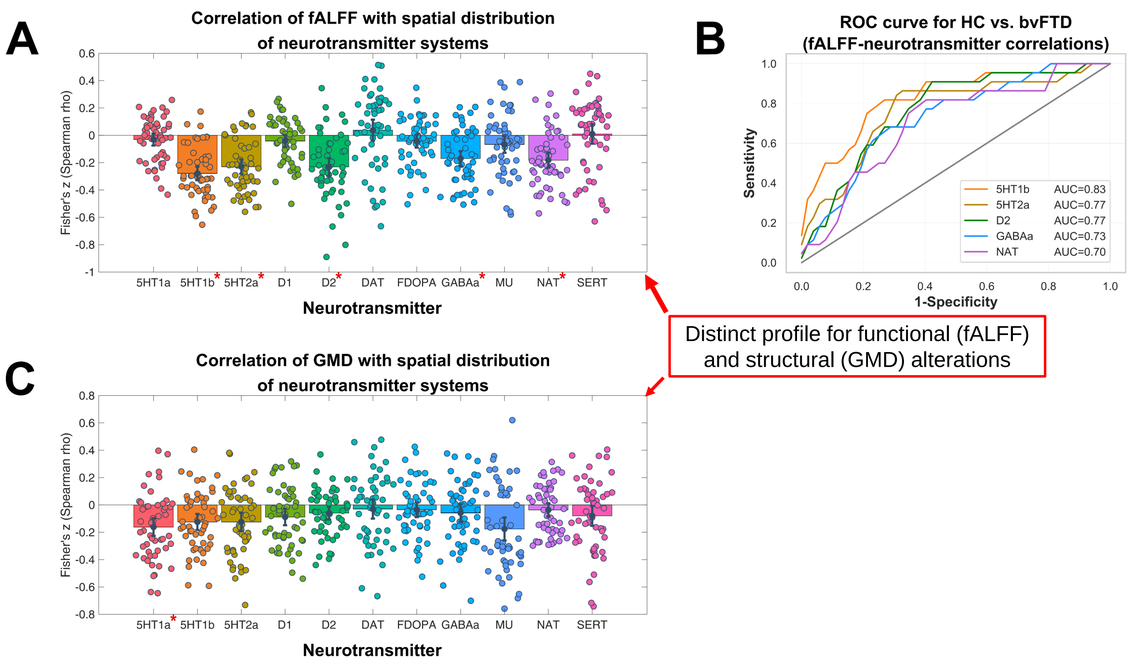
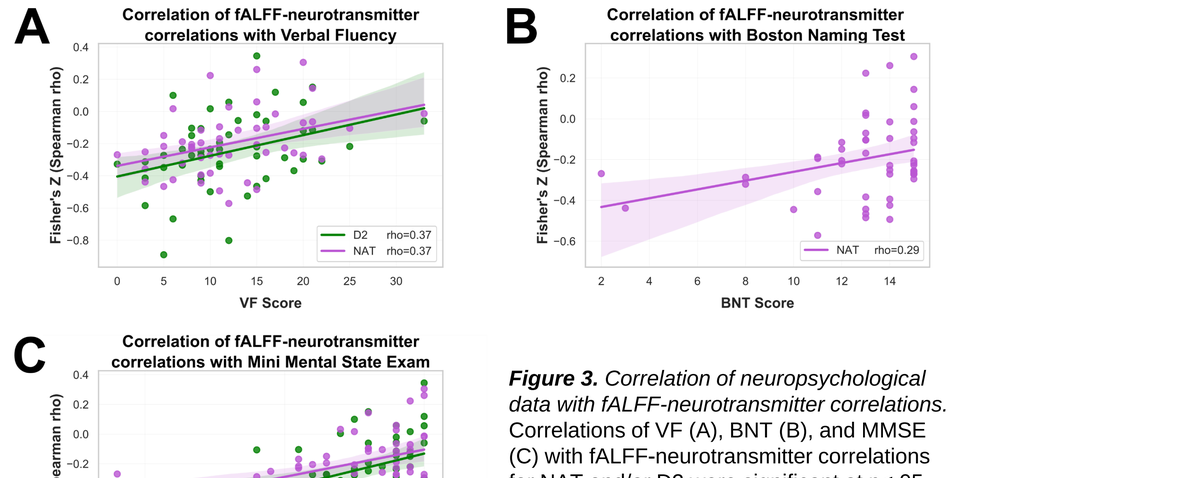


Figure 2. *Correlation with the spatial distribution of neurotransmitter systems.* Correlation of fALFF (A) and GMD (C) with spatial distribution of neurotransmitter systems incl. 95 % confidence interval (error bars). ROC curves (HC vs. FTD) for significant fALFF-neurotransmitter correlations (B). Statistically significant correlations at p<.05 are marked with *.



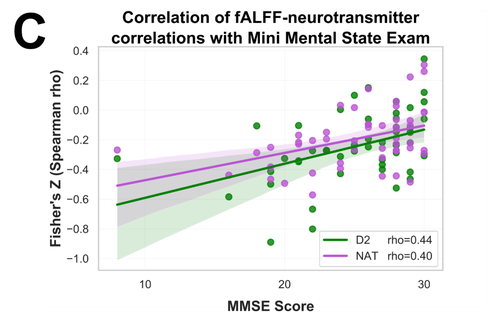


Figure 3. *Correlation of neuropsychological data with fALFF-neurotransmitter correlations.* Correlations of VF (A), BNT (B), and MMSE (C) with fALFF-neurotransmitter correlations for NAT and/or D2 were significant at p<.05 and are displayed incl. bootstrapped 95 % confidence interval.

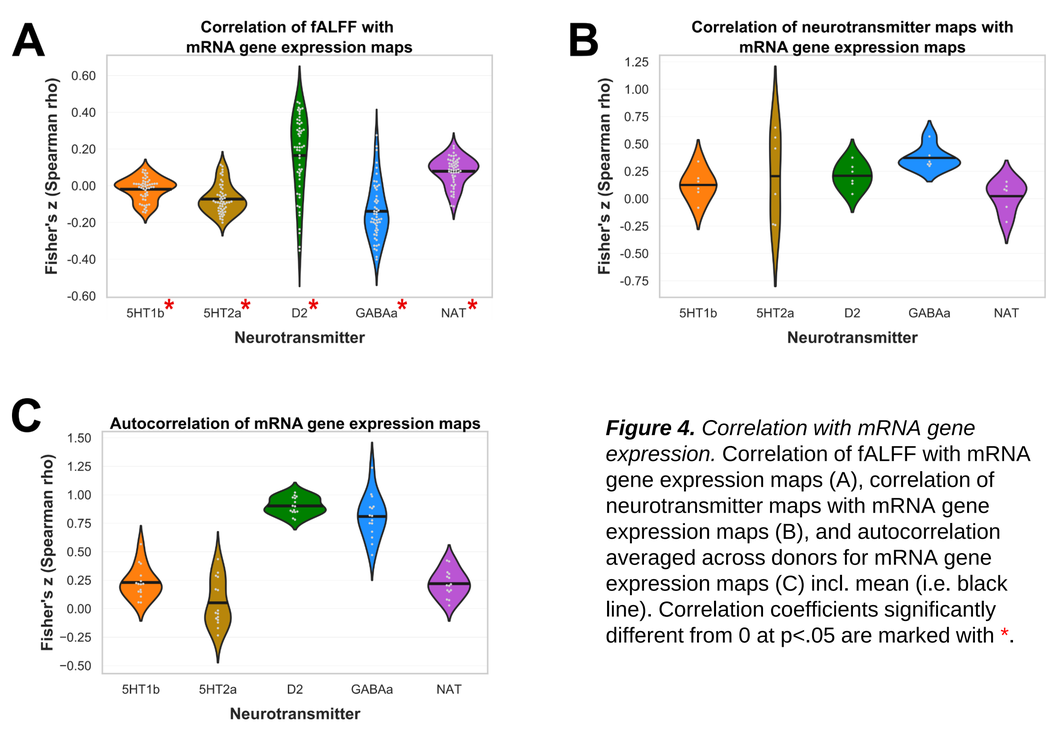


Figure 4. *Correlation with mRNA gene expression.* Correlation of fALFF with mRNA gene expression maps (A), correlation of neurotransmitter maps with mRNA gene expression maps (B), and autocorrelation averaged across donors for mRNA gene expression maps (C) incl. mean (i.e. black line). Correlation coefficients significantly different from 0 at p<.05 are marked with *.

Discussion

- Compared to HC, patients displayed significantly **reduced fALFF in fronto-temporal** and **fronto-parietal** regions (Figure 1)
- **fALFF** alterations **co-localized with** the distribution of **serotonin** (5HT1b, 5HT2a), **dopamine** (D2), and **GABAa receptors**, and the **noradrenaline transporter** (NAT) (Figure 2A)
  → patients showed reduced fALFF signal compared to HC in high density neurotransmitter areas (i.e. negative correlation coefficient)
  → neurotransmitter deficits largely in line with literature [7]
- **fALFF and GMD displayed distinct profiles** for the neurotransmitter correlations (Figure 2A&C)
  → functional (fALFF) alterations unlikely to be driven by structural changes (atrophy)
- **fALFF-neurotransmitter correlations associated with cognitive symptoms** of bvFTD for D2 and NAT (Figure 3A-C)
  → less fALFF reduction in high density neurotransmitter areas (i.e. less negative correlation coefficients) associated with better performance
  → performance in line with previous studies comparing HC and FTD patients [16,17]
- **fALFF** alterations also **co-localized with mRNA expression** of genes encoding the respective receptors and transporters (Figure 4A)
  → 5HT1b, 5HT2a, and GABAa showed negative correlations for both analyses, whereas D2 and NAT displayed opposite correlations in the analyses
  → MENGA correlation coefficients small and autocorrelation very variable
  → more research needed

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