

Mood symptoms in Alzheimer's disease are associated with serotonin-related functional connectivity alterations

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Introduction

People with Alzheimer's disease (AD) and neuropsychiatric symptoms (NPS) have a worse prognosis and their caregivers report greater burden. Several neurotransmitter dysfunctions have been implicated in different mental health conditions, including behavioural alterations in AD [1,2]. However, how neurotransmission may influence brain changes in people with AD and NPS is not clear yet.

Objective

The aim of this study was to investigate **neurotransmitter-related functional brain alterations** associated with the **severity of NPS** in people with AD.

Methods

The sample, recruited from memory clinics at Sheffield Teaching Hospitals (UK) and Kuopio University Hospital (Finland), included 160 older adults (*Table 1*):

- **55 cognitively unimpaired (CU)**
- **75 patients with prodromal to mild AD with NPS (PT-PS)**
- **30 patients without NPS (PT-NP)**

All participants completed a comprehensive neuropsychological, neuropsychiatric (i.e., NPI, GAD-7 and PHQ-9) and MRI assessment.

Resting-state functional MRI scans were pre-processed with the REACT pipeline to extract whole-brain FC maps weighted by the distribution of 13 neurotransmitter receptors and transporters (*Figure 1*).

Table 1 | Demographic, cognitive and neuropsychiatric profiles of the participant groups.

Variables	CU (n = 55)	PT-NP (n = 30)	PT-PS (n = 75)	F	p
Age	67.1 ± 9.7	70.3 ± 8.1	69.0 ± 9.2	1.37	0.259
Education	14.4 ± 2.9	11.7 ± 3.8 ^a	11.5 ± 3.5 ^a	15.36	<0.001
Sex (M/F)	24/31	15/15	31/44	0.65 ^b	0.721
MMSE	28.2 ± 1.5	24.7 ± 4.0 ^a	24.2 ± 4.3 ^a	34.31	<0.001
LM-IR	0.0 ± 1.0	-2.69 ± 1.4 ^a	-2.51 ± 1.5 ^a	82.61	<0.001
LM-DR	0.0 ± 1.0	-3.32 ± 1.8 ^a	-3.45 ± 2.3 ^a	90.45	<0.001
PF	0.0 ± 1.0	-0.82 ± 1.3 ^a	-0.97 ± 1.2 ^a	13.65	<0.001
Stroop time	0.0 ± 1.0	1.98 ± 2.6 ^a	1.43 ± 3.1 ^a	12.90	<0.001
Similarities	0.0 ± 1.0	-1.76 ± 1.8 ^a	-1.69 ± 1.8 ^a	28.35	<0.001
NPI-Q total	--	0.00 ± 0.0	5.20 ± 4.4 ^c	-6.53 ^d	<0.001
PHQ-9	--	3.33 ± 3.7	4.91 ± 5.2	-1.52 ^d	0.132
GAD-7	--	2.47 ± 4.4	3.99 ± 4.4	-1.60 ^d	0.112

CU: Cognitively unimpaired; DR: Delayed recall; F: Female; GAD-7: 7-item Generalized Anxiety Disorder scale; IR: Immediate recall; LM: Logical Memory; M: Male; MMSE: Mini Mental State Examination; NPI-Q: Neuropsychiatric Inventory Questionnaire; PF: Phonemic fluency; PHQ-9: 9-item Patient Health Questionnaire; PT-NP: Patients without neuropsychiatric symptoms; PT-PS: Patients with neuropsychiatric symptoms;
^a Significant difference from CU group
^b Chi-square test
^c Significant difference from PT-NP group
^d Independent-samples t-test

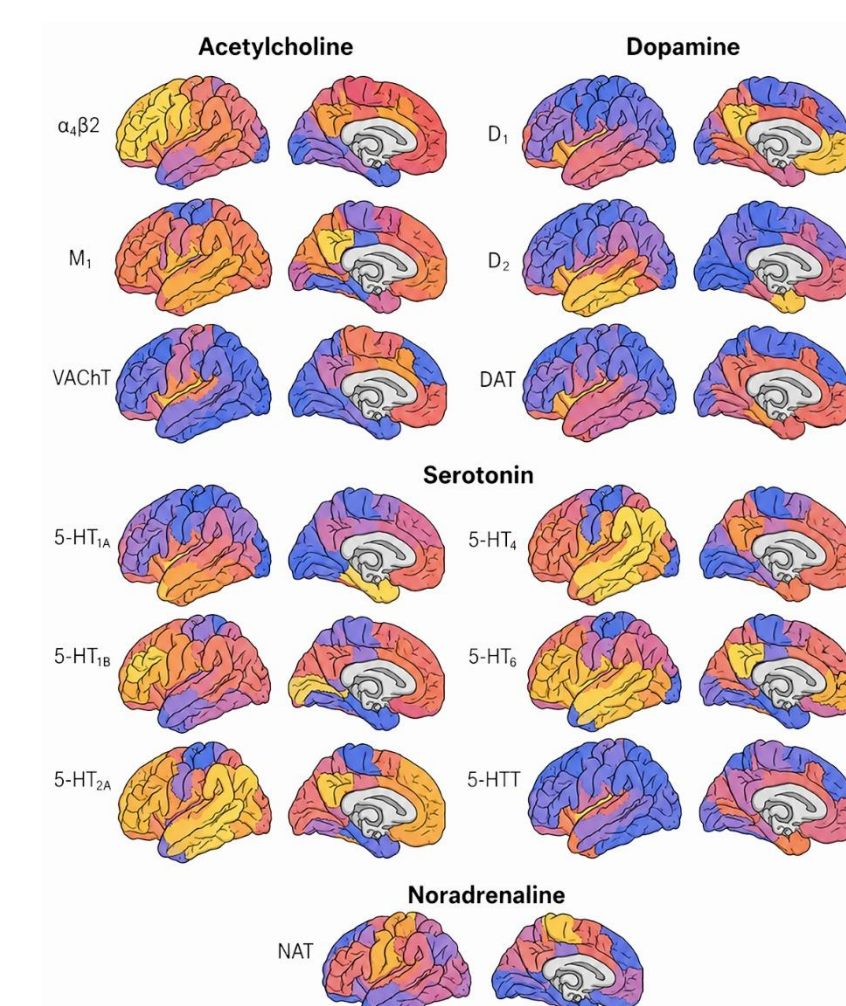


Figure 1 | Neurotransmitter atlases used for REACT.

Voxel-based analyses were carried out in SPM12 to investigate:

- **Between-group differences in neurotransmitter-related FC**
- **Associations between neurotransmitter-related FC and severity of global and affective NPS**

Results

The only significant difference emerged in the comparison between patient groups: FC associated with the **5HT2a receptor** in the **right superior/middle temporal gyrus** was lower in the PT-PS than in the PT-NP group (*Figure 2*).

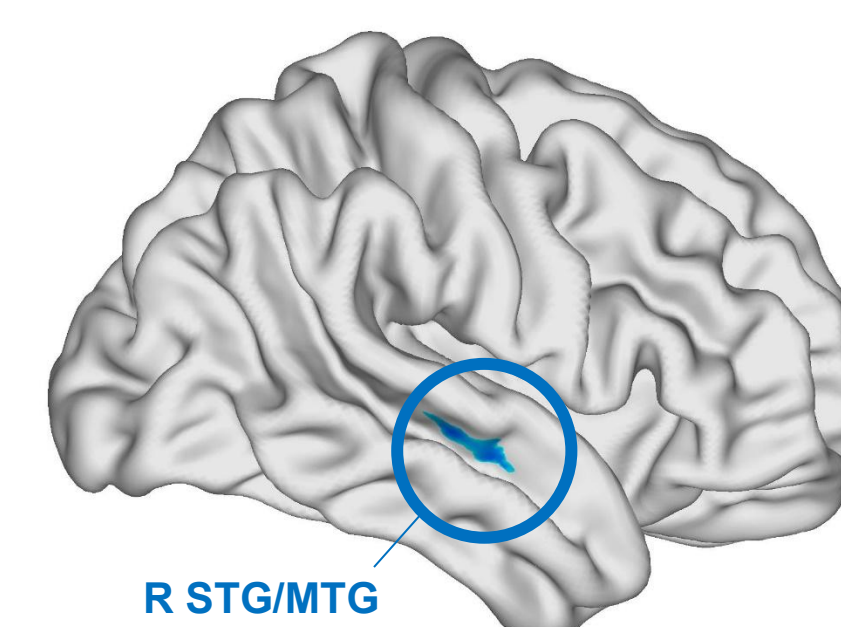


Figure 2 | PT-PS < PT-NP difference in 5HT2a-related FC ($p < 0.05$ FWE-corrected).

Both in the PT-PS group and in the whole patient group (PT-PS + PT-NP):

GAD-7 scores were positively associated with 5HT1a-, 5HT2a- and 5HT4-related FC in **left occipito-temporal regions** and in the **bilateral hypothalamus**. Severity of depression, instead, was negatively correlated with 5HT4- and 5HTT-related FC in the **right middle and inferior temporal gyri** (*Figure 3*).

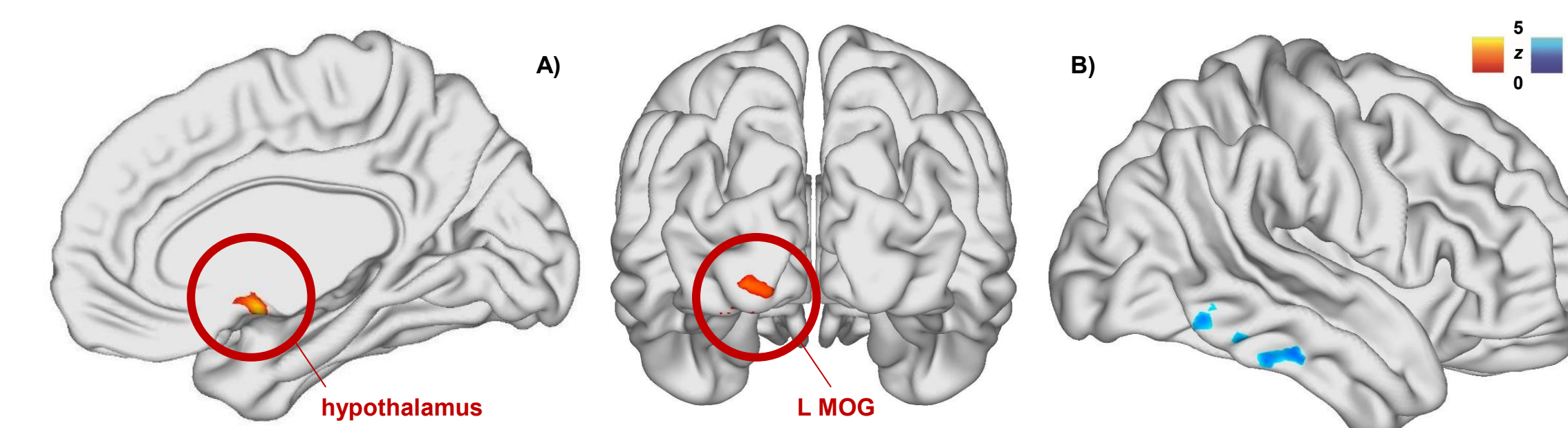


Figure 3 | Positive (red) and negative (blue) associations between 5HT4-related FC and A) GAD-7 and C) PHQ-9 scores in the whole patient group ($p < 0.05$ FWE-corrected).

Conclusions

In AD, severity of affective NPS was associated with alterations in FC weighted by the distribution of serotonergic receptors. This finding is in line with the serotonergic hypothesis of mood disorders [3].

- **Anxiety** was associated with overexpressed 5HT-related FC in occipito-temporal areas (potentially maladaptive) and in the hypothalamus, that is involved in stress responses.
- **Depression**, instead, was associated with weaker FC in right lateral temporal areas [4], possibly due the involvement of these areas in processing self-directed negative stimuli.

Pharmacological interventions targeting the serotonergic system (e.g., vortioxetine [5]) may offer a strategy for managing affective dysregulation in AD. However, further research is needed to determine the most effective 5HT receptor targets.

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