Change in Alzheimer's Disease Gray Matter Cortical Signature is Associated with Treatment Response in Late-Life Depression

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INTRODUCTION

Late-life depression (LLD) presents a growing public health burden.[1] Although many patients respond to first line SSRI or SNRI treatment, only about 30% achieve full remission.[2] For seniors, the timeline for identifying the right medication and dose can be prolonged, especially if multiple medication trials are required. Magnetic Resonance Imaging may offer benefit in optimizing treatment for LLD. Previous work has shown brain morphology, like hippocampal volume or mean cortical thickness, to be associated with antidepressant treatment response.[3]

Alzheimer's disease (AD) gray matter cortical signature is a novel MR-imaging indicator representing mean cortical thickness of nine regions of interest (Figure 1).[4,5] Atrophy in AD cortical signature has been associated with progression of dementia, endorsing its value as a predictive factor of early neurodegeneration.[4,5]

Dementia and depression in late life often overlap clinically and many studies support the bidirectionality in their longitudinal relationship.[6] And although cortical atrophy is reported in both dementia and depression,[3,7] the predictive value of AD cortical signature in late life antidepressant treatment has not been reported.

This study sought to examine the relationship between AD cortical signature and response to LLD treatment.

DATA ACQUISITION

Screening
- 60 years old and older
- Current MADRS score ≥ 12
- Exclusion criteria: unstable or unmanaged medical condition, dementia, history of stroke, epilepsy, bipolar disorder, schizophrenia, psychosis, mania, current or recent substance abuse, suicidal ideation, magnetic metal in body

Baseline visit (pre-treatment)
- Structural 3T or 7T MRI scan
- MADRS assessment
- Neuropsychological battery
- Health history
- Random assignment of monoaminergic antidepressant (escitalopram or levomilnacipran)

Treatment
- Standard course of antidepressant therapy
- Check-ins & dosage adjustment as clinically indicated
- Data collection for whole NEMO study
- Attrition

Week 12 (post-treatment)
- Structural 3T or 7T MRI scan
- MADRS assessment
- Neuropsychological battery
- Health history
- Final N=39, mean age of sample = 68 years

DATA PROCESSING

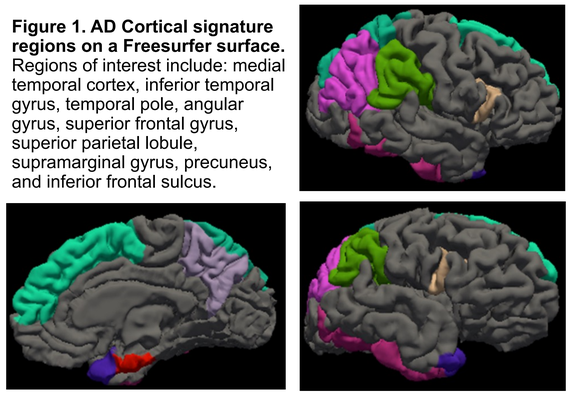
Structural Preprocessing[8-10]
All MRI scans undergo SPM Preprocessing Pipeline

Segmentation & Quality Control[8-10]
Freesurfer processing auto-segmentation protocol applied. Manual quality checking of auto-segmentation for all scans; addition of control points & adjustment of Freesurfer processing parameters to optimize segmentation.

Extraction and Categorization
Brain volume data extracted from Freesurfer segmentation end-products. Participant categorized as responder or non-responder (responder: MADRS score reduction ≥50% from baseline to week 12 OR Week 12 MADRS score <10).

Data Harmonization[11,12]
Because imaging was collected on 3T and 7T MR scanners, ComBat regional harmonization was applied across scanners to reduce scanner effects.

Figure 1. AD Cortical signature regions on a Freesurfer surface. Regions of interest include: medial temporal cortex, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobule, supramarginal gyrus, precuneus, and inferior frontal sulcus.



STATISTICAL ANALYSIS

Group demographic differences were assessed with paired t-tests (α=0.05)—only week 12 MADRS score, percent change in MADRS, and percent change in AD cortical signature were significantly different between responders and non-responders (Table 1 & Figure 2).

Between-subject effects at baseline: linear regression model (Results, Table 2). Dependent variable: baseline AD cortical signature. Fixed effects: responder status (responder/non-responder), drug (levomilnacipran/escitalopram), sex (M/F), and field strength (3T/7T).

To assess morphological change over time, the model was repeated but with the dependent variable replaced with the baseline AD cortical signature subtracted from its week 12 value, and with the addition of baseline AD cortical signature as a fixed effect (Table 3).

Statistical analyses were conducted in SPSS Statistics 26 (IBM, 2019).

RESULTS

Table 1. Demographics & paired t-tests

Factor	Whole Group	Responders	Non-responders	Paired t-test
Age (years)	68 (7)	66 (5)	69 (9)	t(37)=-1.3, p=0.191
Sex (# F)	23 (59%)	16 (67%)	7 (47 %)	χ^2=1.5, p=0.217
Race (# White)	31 (79%)	20 (83%)	11 (73%)	χ^2=0.6, p=0.452
Education (years)	16 (3)	16 (2)	16 (3)	t(31)=0.3, p=0.756
CIRSG	10 (4)	10 (4)	11 (4)	t(35)=-0.8, p=0.420
Field Strength (# 7T)	24 (62%)	14 (58%)	10 (67%)	χ^2=0.3, p=0.603
Baseline MADRS	22 (6)	21 (5)	24 (7)	t(34)=-1.3, p=0.190
Week 12 MADRS	**8 (8)**	**5 (4)**	**19 (7)**	**t(28)=-6.6, p<0.001**
MADRS % change	**63 (27)**	**75 (20)**	**29 (14)**	**t(26)=5.7, p<0.001**
Baseline RBANS	99 (13)	100 (12)	97 (15)	t(16)=0.7, p=0.48
ICV baseline (cm^3)	1409 (195)	1402 (175)	1421 (231)	t(37)=-0.3, p=0.766
Baseline AD cortical signature	2.5 (0.13)	2.5 (0.15)	2.5 (0.08)	t(35)=-0.2, p=0.825
Week 12 AD cortical signature	2.5 (0.16)	2.5 (0.14)	2.4 (0.20)	t(21)=1.5, p=0.148
AD cortical signature % change	**0.8 (4.7)**	**0.34 (3.2)**	**-4.9 (7.1)**	**t(21)=-2.5, p<0.05**
WMH (mm^3)	3357 (3056)	3203 (1930)	3641 (4554)	t(35)=-0.4, p=0.683

CIRSG – cumulative illness rating scale for geriatrics, MADRS – Montgomery-Åsberg Depression Rating Scale, post-treatment refers to week 12, % change is always pre- minus post-treatment, ICV – intracranial volume, AD – Alzheimer's disease, WMH – white matter hyperintensities, RBANS – Repeatable Battery for the Assessment of Neuropsychological Status. **Bolded values indicate significant group differences.**

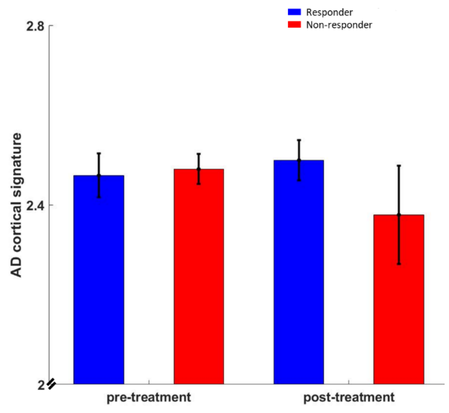


Figure 2. Pre- and post-treatment AD cortical signature. Responders are shown in blue and non-responders are shown in red. Non-responders showed significant declines from pre- to post-treatment as compared to responders who showed no change.

RESULTS

Table 2. Baseline AD cortical signature and clinical factors

Factor	Baseline AD Cortical Signature	Baseline AD Cortical Signature (ComBat)
Response (Ref=Responders)	B= 0 (0), ß= 0, t= 0	B= 0 (0), ß= 0, t= 0
Drug (Ref=Escitalopram)	B= 0.1 (0.1), ß= 0.26, t= 1.6	B= 0.1 (0.1), ß= 0.32, t= 1.6
MR Field Strength (Ref=7T)	**B= 0.2 (0.1), ß= 0.64, t= 2.8***	B= 0 (0.1), ß= 0.15, t= 0.6
Age	B= 0 (0), ß= -0.07, t= -0.4	B= 0 (0), ß= -0.09, t= -0.5
Sex (Ref=M)	B= 0.1 (0), ß= 0.27, t= 1.5	B= 0.1 (0), ß= 0.31, t= 1.5
Baseline MADRS	B= 0 (0), ß= 0.15, t= 0.8	B= 0 (0), ß= 0.19, t= 0.8
ICV	B= 0 (0), ß= -0.07, t= -0.3	B= 0 (0), ß= -0.08, t= -0.3

B – not scaled regression coefficient, ß – scaled regression coefficient.
Significant values (p<0.05) are in bold.

Table 3. Change in AD cortical signature and clinical factors

Factor	Change in AD Cortical Signature	Change in AD Cortical Signature (ComBat)
Response (Ref=Responders)	**B= -0.2 (0.1), ß= -0.67, t= -2.8***	**B= -0.2 (0.1), ß= -0.68, t= -3.0***
Drug (Ref=Escitalopram)	B= 0 (0.1), ß= -0.11, t= -0.4	B= 0 (0.1), ß= -0.15, t= -0.6
MR Field Strength (Ref=7T)	B= 0 (0.1), ß= 0.08, t= 0.2	B= 0 (0.1), ß= 0.07, t= 0.2
Age	B= 0 (0), ß= -0.37, t= -1.8	B= 0 (0), ß= -0.38, t= -2
Sex (Ref=M)	B= -0.1 (0.1), ß= -0.49, t= -2.1	**B= -0.1 (0.1), ß= -0.53, t= -2.4***
Baseline MADRS	B= 0 (0), ß= 0.16, t= 0.7	B= 0 (0), ß= 0.13, t= 0.6
ICV	B= 0 (0), ß= -0.26, t= -0.7	B= 0 (0), ß= -0.28, t= -0.8
Baseline AD Cortical Signature	B= 0 (0.3), ß= -0.02, t= -0.1	B= 0 (0.3), ß= 0.05, t= 0.2

B – not scaled regression coefficient, ß – scaled regression coefficient.
Significant values (p<0.05) are in bold.

CONCLUSIONS

- In LLD treatment, AD cortical signature was associated with responder status: individuals who responded had no change in AD cortical signature (following ComBat), however non-responders showed a decline in AD cortical signature (4.9% decrease on average at 12 weeks).
- It may be that effective pharmacotherapy in LLD prevents further decline in cortical thickness, as antidepressant treatment has been reported to reverse atrophy. More likely, individuals with more severe cortical thickness loss are less likely to respond to the pharmacotherapy interventions used in this study.
- Thus, AD signature may be a useful predictor in determining treatment nonresponse in LLD.

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