# Severity of Symptoms Is Associated with Accelerated Brain Aging in Depressive Patients

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## INTRODUCTION

Deviation between chronological age and **brain-based age prediction** has frequently been used as an indicator of disease risk and severity[1,2].

Currently, most brain age research has focused on a global whole-brain approach[3]. We trained a **regional brain age model** on a large cohort of **healthy subjects** using the 69 regions of the **Harvard Oxford** cortical and subcortical atlas.

Applying the regional brain age model to **depressive patients**, we associate their **acute symptom severity** as well as **cumulative disease severity** with the regional **brain-PAD** scores.

**Acute symptom severity** was measured using the **Beck's Depressive Inventory**.

**Cumulative disease severity** was measured by the number of **hospitalizations** due to their mental illness.

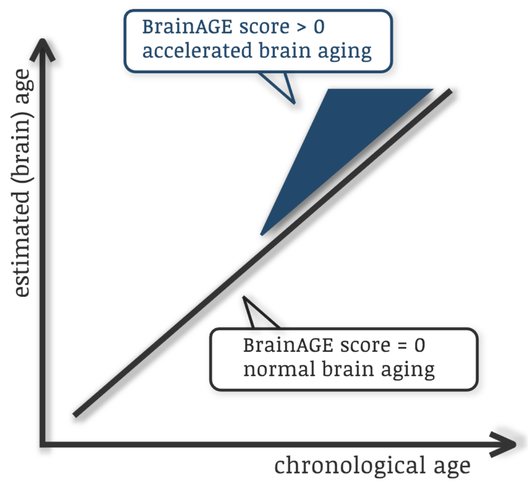


**Figure 1.** The BrainAGE score (or brain-PAD) is defined as the difference between estimated and chronological age. Accelerated brain aging results in a higher score, depicted in blue as a higher regression slope. Illustration adapted from [5].

## METHODS

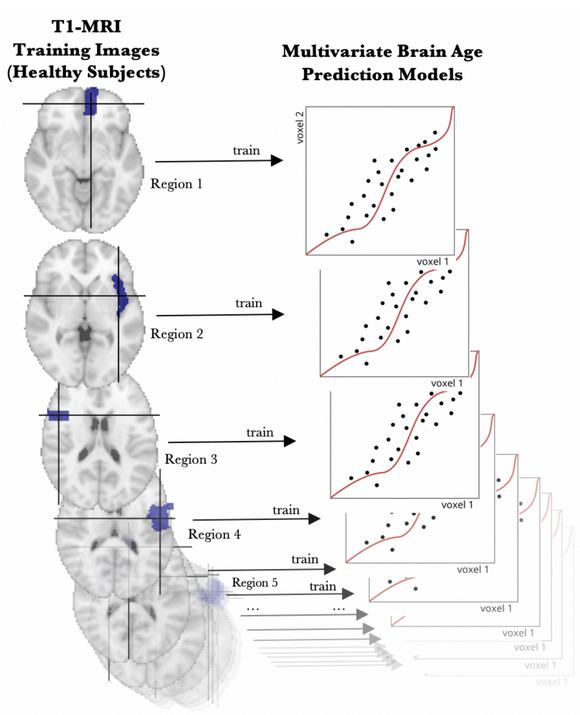


**Figure 2.** Regional brain age prediction based on every region of the Harvard Oxford atlas..

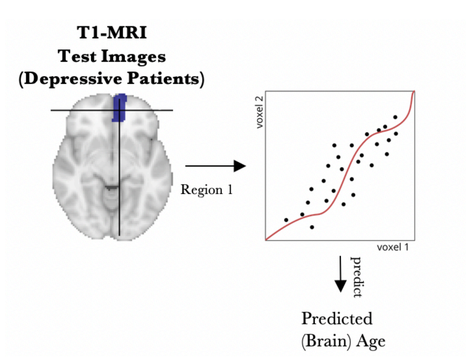


**Figure 3.** Application of regional brain age models to predict brain age in depressive patients.

*Brain Age Model*

We trained a **LinearSVR** predicting chronological age on a sample of 1598 healthy subjects for every region of the **Harvard Oxford** atlas using the **PHOTON**[4] toolbox. We then predicted regional brain age for an independent sample of **depressive patients**.

*Structural MRI Data*

We pre-processed the structural MRI data using the SPM **VBM8 toolbox** to extract grey matter density maps.

*Bayesian Hierarchical Modelling*

We modelled the effect of symptom severity on regional brain age acceleration with a Bayesian Hierarchical model using brms.

Table 1
*Sample description: Hospitalization*

| | N = 524 | age | | | hospitalization | | |
|---|---|---|---|---|---|---|---|
| | | mean | sd | range | mean | sd | range |
| male | 193 | 36.65 | 13.76 | 18-65 | 1.81 | 1.95 | 0-12 |
| female | 331 | 37.78 | 13.39 | 18-65 | 1.58 | 2.21 | 0-17 |

*Note: N = sample size, sd = standard deviation.*

Table 2
*Sample description: BDI*

| | N = 513 | age | | | BDI | | |
|---|---|---|---|---|---|---|---|
| | | mean | sd | range | mean | sd | range |
| male | 188 | 36.95 | 13.70 | 18-65 | 18.60 | 10.51 | 0-46 |
| female | 325 | 37.50 | 13.30 | 18-64 | 17.92 | 11.55 | 0-52 |

*Note: N = sample size, sd = standard deviation, BDI = Beck's Depression Inventory.*

## RESULTS

Table 3
*Results of the Bayesian Hierarchical Model: Hospitalization*

| | | Estimate | Est. Error | lower CI | upper CI | Eff. Sample | Rhat |
|---|---|---|---|---|---|---|---|
| Group-Level Effects: | sd (Intercept) | 0.93 | 0.10 | 0.75 | 1.13 | 4427 | 1.00 |
| ~region (Number of levels: 69) | sd (BDI) | 0.19 | 0.09 | 0.03 | 0.37 | 2053 | 1.00 |
| | sd (Age) | 1.58 | 0.15 | 1.32 | 1.90 | 5313 | 1.00 |
| | cor (Intercept, BDI) | 0.27 | 0.27 | -0.31 | 0.76 | 14396 | 1.00 |
| | cor (Intercept, Age) | 0.30 | 0.13 | 0.03 | 0.53 | 3736 | 1.00 |
| | cor (BDI_Age) | 0.39 | 0.25 | -0.14 | 0.83 | 564 | 1.00 |
| Group-Level Effects: ~Subject_ID (Number of levels: 524) | sd (Intercept) | 4.32 | 0.14 | 4.05 | 4.61 | 2316 | 1.00 |
| Population-Level Effects: | Intercept | -0.61 | 0.22 | -1.04 | -0.18 | 1634 | 1.00 |
| | BDI | 0.56 | 0.20 | 0.17 | 0.96 | 1748 | 1.00 |
| | Age | -7.15 | 0.28 | -7.70 | -6.60 | 2263 | 1.00 |
| | ROI Size | 0.02 | 0.12 | -0.22 | 0.26 | 7876 | 1.00 |
| | Mean Abs PAD | -0.00 | 0.13 | -0.25 | 0.25 | 5697 | 1.00 |
| Family Specific Parameters: | sigma | 7.61 | 0.05 | 7.51 | 7.70 | 16287 | 1.00 |
| | nu | 4.09 | 0.09 | 3.91 | 4.28 | 19712 | 1.00 |

*Note: sd = standard deviation, cor = correlation, CI = 95% confidence interval, PAD = Predicted Age Deviation*

Table 4
*Results of the Bayesian Hierarchical Model: BDI*

| | | Estimate | Est. Error | lower CI | upper CI | Eff. Sample | Rhat |
|---|---|---|---|---|---|---|---|
| Group-Level Effects: | sd (Intercept) | 0.95 | 0.10 | 0.77 | 1.17 | 3391 | 1.00 |
| ~region (No. of levels: 69) | sd (BDI) | 0.16 | 0.09 | 0.01 | 0.34 | 2146 | 1.00 |
| | sd (Age) | 1.63 | 0.15 | 1.36 | 1.95 | 3088 | 1.00 |
| | cor (Intercept, BDI) | 0.33 | 0.29 | -0.33 | 0.82 | 8306 | 1.00 |
| | cor (Intercept, Age) | 0.33 | 0.12 | 0.07 | 0.56 | 2527 | 1.00 |
| | cor (BDI_Age) | 0.02 | 0.28 | -0.58 | 0.57 | 395 | 1.01 |
| Group-Level Effects: ~subjects (No. of levels: 513) | sd (Intercept) | 4.38 | 0.15 | 4.11 | 4.69 | 1336 | 1.00 |
| Population-Level Effects: | Intercept | -0.59 | 0.23 | -1.04 | -0.15 | 1355 | 1.00 |
| | BDI | 0.40 | 0.20 | 0.02 | 0.78 | 1196 | 1.00 |
| | Age | -6.97 | 0.29 | -7.53 | -6.40 | 1140 | 1.00 |
| | ROI Size | 0.01 | 0.12 | -0,24 | 0.25 | 4279 | 1.00 |
| | Mean Abs PAD | -0.01 | 0.13 | -0.26 | 0.25 | 3832 | 1.00 |
| Family Specific Parameters: | sigma | 7.59 | 0.05 | 7.49 | 7.70 | 10874 | 1.00 |
| | nu | 4.10 | 0.09 | 3.92 | 4.28 | 9994 | 1.00 |

*Note: sd = standard deviation, cor = correlation, CI = 95% confidence interval, PAD = Predicted Age Deviation*

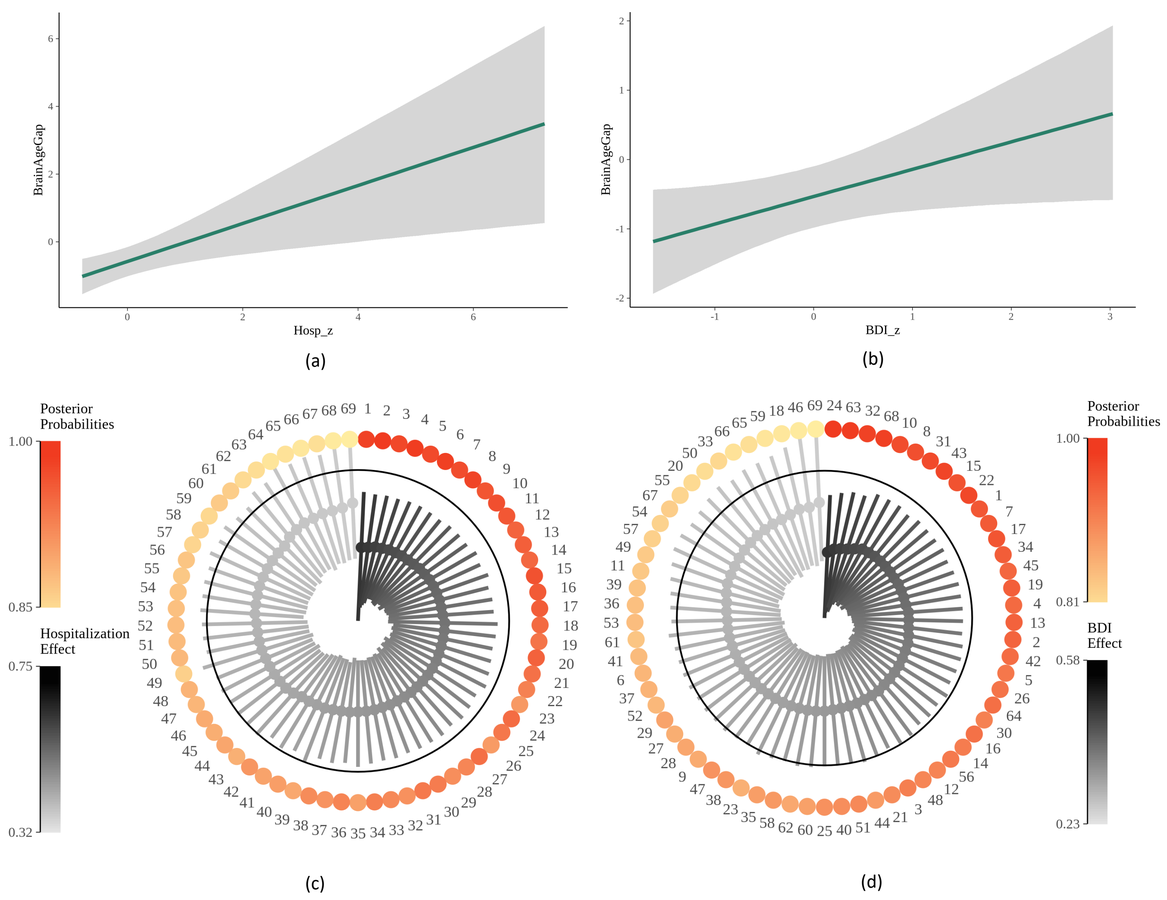


**Figure 4.** Overall marginal effect of hospitalization **(a)** and BDI **(b)** induced brain age acceleration. **(c)** and **(d)** show Hospitalization- and BDI-related regional brain age acceleration effect for each of the 69 regions in the HO atlas. Grey bars indicate the Hospitalization and BDI effect on brain-PAD (whiskers represent 90% Bayesian credible interval). Black circle represents a zero-effect. Colored circles show the Bayesian posterior probability of the Hospitalization and BDI effect to be larger than zero.

(1) Inferior Frontal Gyrus pars opercularis, (2) Frontal Orbital Cortex, (3) Left Cerebral Cortex , (4) Occipital Pole, (5) Central Opercular Cortex, (6) Precentral Gyrus, (7) Right Cerebral Cortex , (8) Left Thalamus, (9) Frontal Pole, (10) Frontal Medial Cortex, (11) Inferior Frontal Gyrus pars triangularis, (12) Supramarginal Gyrus posterior division, (13) Parietal Operculum Cortex, (14) Left Putamen, (15) Insular Cortex, (16) Middle Temporal Gyrus temporooccipital part, (17) Right Lateral Ventricle, (18) Postcentral Gyrus, (19) Left Accumbens, (20) Middle Temporal Gyrus posterior division, (21) Right Caudate, (22) Heschl s Gyrus includes H1 and H2 , (23) Left Cerebral White Matter, (24) Cingulate Gyrus posterior division, (25) Frontal Operculum Cortex, (26) Supramarginal Gyrus anterior division, (27) Cingulate Gyrus anterior division, (28) Left Lateral Ventrical, (29) Parahippocampal Gyrus posterior division, (30) Occipital Fusiform Gyrus, (31) Left Caudate, (32) Superior Temporal Gyrus posterior division, (33) Right Cerebral White Matter, (34) Lingual Gyrus, (35) Planum Polare, (36) Temporal Occipital Fusiform Cortex, (37) Right Thalamus, (38) Precuneous Cortex, (39) Middle Temporal Gyrus anterior division, (40) Paracingulate Gyrus, (41) Planum Temporale, (42) Subcallosal Cortex, (43) Middle Frontal Gyrus, (44) Left Amygdala, (45) Angular Gyrus, (46) Temporal Pole, (47) Cuneal Cortex, (48) Superior Parietal Lobule, (49) Right Accumbens, (50) Parahippocampal Gyrus anterior division, (51) Inferior Temporal Gyrus temporooccipital part, (52) Right Hippocampus, (53) Temporal Fusiform Cortex posterior division, (54) Right Amygdala, (55) Superior Temporal Gyrus anterior division, (56) Right Putamen, (57) Left Hippocampus, (58) Superior Frontal Gyrus, (59) Inferior Temporal Gyrus posterior division, (60) Lateral Occipital Cortex superior division, (61) Juxtapositional Lobule Cortex formerly Supplementary Motor Cortex , (62) Intracalcarine Cortex, (63) Left Pallidum, (64) Inferior Temporal Gyrus anterior division, (65) Temporal Fusiform Cortex anterior division, (66) Lateral Occipital Cortex inferior division, (67) Supracalcarine Cortex, (68) Right Pallidum, (69) Brain Stem

## DISCUSSION

The Hierarchical Bayesian model revealed a significantly accelerated brain aging effect of **cumulative disease severity in 59 regions** and **acute symptom severity in 31 regions** of the Harvard Oxford atlas.

The **region-based brain age prediction approach** advances on the current whole-brain modelling and provides the possibility to study the spatial patterns of brain aging.

Importantly, we find accelerated brain aging effects for **subjective, self-rated symptom severity** as well as for an objective measurement of disease severity over the lifespan.

The arisen **spatial pattern differences** still need to be explored to investigate the differential effect of acute and cumulative symptom and disease severity.

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