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Machine-learning based brain age estimation in major depression showing no evidence of accelerated aging

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ABSTRACT

Molecular biological findings indicate that affective disorders are associated with processes akin to accelerated aging of the brain. The use of the BrainAGE (brain age estimation gap) framework allows machine-learning based detection of a gap between age estimated from high-resolution MRI scans an chronological age, and thus an indicator of systems-level accelerated aging. We analysed 3T high-resolution structural MRI scans in 38 major depression patients (without co-morbid axis I or II disorders) and 40 healthy controls using the BrainAGE method to test the hypothesis of accelerated aging in (non-psychotic) major depression. We found no significant difference (or trend) for elevated BrainAGE in this pilot sample. Unlike previous findings in schizophrenia (and partially bipolar disorder), unipolar depression per se does not seem to be associated with accelerated aging patterns across the brain. However, given the limitations of the sample, further study is needed to test for effects in subgroups with comorbidities, as well as longitudinal designs.

1. Introduction

Accelerated biological aging has been hypothesized in several psychiatric disorders, such as affective, psychotic, and trauma-related disorders (Darrow et al., 2016; Wolkowitz, 2018). This also includes major depression, for which several recent lines of evidence suggest an accelerated course of cellular and cerebral aging. On a molecular level, the interaction of cellular stress, neuro-plasticity and age-dependent changes has been of particular interest (Sibille, 2013). Several studies have reported an association between depression a leukocyte site telomere length, with can be extracted from peripheral blood samples (Schutte and Malouff, 2015). Telomere length might be related to various environmental risk factors such as early life stress, which act across diagnosis but again might be particularly relevant in depression (Darrow et al., 2016; Price et al., 2013; Verhoeven et al., 2014).

On a network or neural-systems level (i.e. macroscopic level of brain regions and/or the whole brain), there is now also evidence linking aging to depression as well as other psychiatric conditions (Koutsouleris et al., 2014). Analysis of brain structural variation has demonstrated an anatomical overlap of regions displaying changes across healthy aging as well as vulnerability to psychotic and neurodegenerative disorders (Douaud et al., 2014). In major depression, two areas in particular have been implicated in accelerated aging. In a cohort of elderly adults Elbejjani et al. demonstrated, that depressive symptoms are associated with larger hippocampal grey matter loss, as was history of major depression, while treatment for depression decelerated this decline (Elbejjani et al., 2015). Another study in a sample of patients with major depressive disorder (MDD) demonstrated in a cross-sectional study, that putamen volume showed a steeper decline in patients than in controls, i.e. group by age interaction (Sacchet et al., 2017). The limitation of previous studies is related to the limited assessment of single brain regions, rather than the entire brain, and to the application of univariate statistical approaches only. In contrast, multivariate statistics take into account a wealth of parameters, aiming to extract meaningful patterns (rather than singular parameters), which best describe or predict a phenomenon like accelerated aging.

In this present pilot study, we used BrainAGE (brain age gap estimate) to test the hypothesis, that major depression is associated with a systems-level signature of accelerated brain aging. While there has been at least one previous study using BrainAGE in (amongst others) a MDD cohort (Koutsouleris et al., 2014), there is currently lack of replication and also a lack of understanding whether MDD patients (without co-

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morbidities) would show increased BrainAGE as a putative marker of accelerated aging.

The BrainAGE indicator is based on a voxel-wise analysis of structural MRI scans and uses a machine learning protocol to estimate the age of an individual brain based on the MRI scan and integrating the information across all grey-matter voxels (Franke et al., 2010; Gaser et al., 2013). Integrating multi-variate statistics into a singular value, the actual chronological age is then subtracted from this score in order to derive a metric of accelerated (or delayed) aging. This parameter has been applied in several studies (Franke et al., 2013; Gaser et al., 2013; Hajek et al., 2019), and we recently showed using BrainAGE that schizophrenia, but not bipolar affective disorder was associated with accelerated aging, as compared to healthy controls and across disorders (Nenadic et al., 2017). Hence, replication of initial studies (Koutsouleris et al., 2014) is needed.

2. Methods

2.1. Sample

We recruited patients meeting DSM-IV criteria for major depression ($n = 38$) and psychiatrically healthy control subjects from the local community ($n = 40$), which were matched for age (ANOVA, $p = 0.318$) and gender (chi square test, $p = 0.624$). Prior to study participation, all subjects provided written informed consent to a study protocol approved by the ethics committee of the Friedrich-Schiller-University of Jena Medical School.

MDD patients were recruited from the in-patient and out-patient services of Jena University hospital. They underwent a full clinical SKID-I interview by a psychiatrist (B.B.), who assured that they all met criteria for current or previous major depressive episodes, and thus had either single major depressive episodes or recurrent MDD. None of these patients had a co-morbid axis I psychiatric disorder and they were all screened for absence of an axis II disorder / personality disorder, which was further assured by chart reviews. None of the MDD patients had psychotic symptoms.

Healthy control subjects were also screened by a psychiatrist (B.B.) to ensure absence of a current or previous psychiatric disorder or psychotherapeutic treatment.

None of the study participants had a n untreated major medical condition (e.g. uncontrolled hypertension or diabetes), a current or previous central neurological disease, traumatic brain injury with loss of consciousness > 5 min, or learning disability. In addition, none of the subjects was suffering from clinical obesity.

Clinical and demographic characteristics are given in Table 1.

Table 1
Clinical and demographic characteristics of sample.

	Major depressive disorder (MDD) patients	Healthy controls (HC)
N	38	40
(female / male)	(21 f / 17 m)	(20 f / 20 m)
Mean age in years (SD)	45.65 (15.68)	42 (13.17)
Age range	19 – 66 years	21 – 73 years
First-episode / multiple episodes	$n = 9$ first episode, $n = 29$ recurrent episodes	
Concurrent depressive symptoms: mean BDI score (SD)	24.19 (10.64) ange: 3–42	
Psychotropic medication	$n = 27$ patients with long-term medication (>14d) $n = 5$ patients with short term medication (<14d) $n = 6$ off medication	

2.2. Magnetic resonance image (MRI) acquisition and analysis

Using a 3 Tesla Siemens Prisma fit scanner, we obtained T1-weighted MPRAGE (TR 2300 ms, TE 2.07 ms, α 9°, 192 contiguous sagittal slices, in-plane field of view 256 mm, voxel resolution 1 × 1 × 1 mm; 5:21 min acquisition time) for each participant. Scans were visually inspected for artefacts and in addition they passed the automated quality assurance protocol implemented in VBM8 software (http://dbm.neuro.uni-jena.de/vbm8).

We pre-processed MRI scans using the BrainAGE protocol (Franke et al., 2010), as previously described in a recent analysis of schizophrenia and bipolar disorder patients (Nenadic et al., 2017). This included correction for field inhomogeneities, spatial normalisation and segmentation using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) und the SPM8 software (http://www.fil.ion.ucl.ac.ik/spm/) running under Matlab. Finally we applied affine spatial registration and Gaussian smoothing with 4 mm full-width-at-half-maximum (FWHM) and resampled data to 4 mm.

For BrainAGE calculation, we applied a relevance vector regression (RVR; (Tipping, 2001)), as described previously. Details have been reported in our previous publications on BrainAGE (Nenadic et al., 2017). We used 743 healthy controls subjects (mean age: 43.93 y; 316 male, 427 female) of the IXI (https://brain-development.org/ixi-dataset/) and OASIS (https://www.oasis-brains.org/) databases for training of our BrainAGE framework. In order to adjust for scanner effects, we estimated the quadratic age trend of BrainAGE using the healthy control subjects and removed this trend from all BrainAGE estimates.

2.3. Statistical analysis

For statistical analysis, we considered a two-sample T-test with $P < 0.05$ to assess group differences between the MDD patients and healthy controls.

Given the limited sample size, we also used G*Power 3.1 to perform a post hoc calculation of the achieved power.

3. Results

MDD patients and healthy controls did not differ in age or gender distribution.

Mean BrainAGE scores of MDD patients and healthy controls did not differ significantly ($p = 0.63$), see also Table 2.

G*Power calculation showed that with a one-tailed t-test with groups of $n = 38$ and $n = 40$, respectively, and an alpha error of 0.05, the power of this sample would amount to 0.968 for a large effect size (Cohen's $d = 0.8$), and 0.706 for a medium effect size (Cohen's $d = 0.5$), respectively (Fig. 1) .

Table 2
BrainAGE scores in patients with major depressive disorder (MDD) vs. healthy controls (HC).

BrainAGE scores	Major depressive disorder (MDD) patients	Healthy controls (HC)
Mean	0.412	0.00
Median	0.438	−0.596

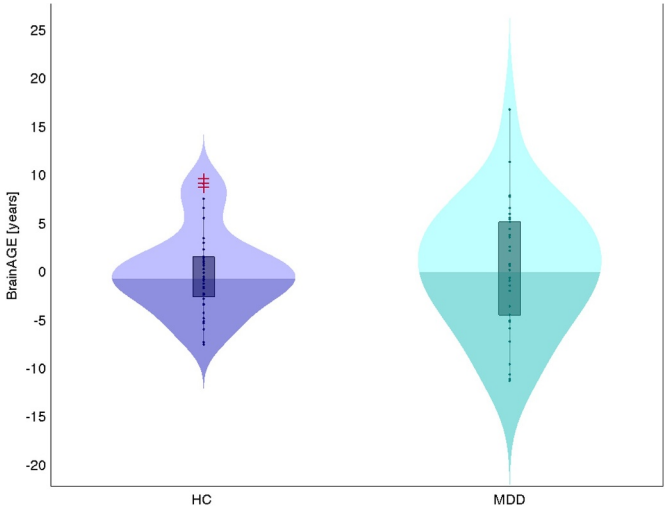

Fig. 1. Violin plot of the distribution of BrainAGE (brain age estimation gap) scores for patients with major depressive disorder (MDD) vs. psychiatrically healthy controls (HC). The group difference was not significant (*t*-test, $p = 0.63$).

4. Discussion

Our findings do not support accelerated aging in major depression to be observable applying the BrainAGE approach. While our post-hoc power estimation indicates that sample sizes might have been too small to detect small effects, it still shows that more robust larger effect sizes would have been detectable with >0.9 power. However, this limitation in sample size also precluded further analysis of subsamples within the MDD group: if BrainAGE changes were only present in a subgroup of MDD patients, these might not have been detected in a simple group comparison.

While the overall negative finding does not generally argue against the possibility of accelerated aging in MDD in single brain regions or on the molecular level (e.g. single brain areas or cell types might show accelerated aging in MDD undetected by the BrainAGE framework applied here), our results do not support accelerated aging to be related to MDD on a (macroscopic) systems or brain-wide level. In our interpretation of these findings, we aim to link both systems-level and molecular findings with regards to regional vs. global brain aging in MDD, and shall discuss the effects of psychiatric vs. non-psychiatric factors on BrainAGE, as well as limitations of our study design.

Unlike a previous study including MDD patients showing increased BrainAGE in MDD relative to healthy controls (Koutsouleris et al., 2014) and previous positive studies in schizophrenia and mixed findings in bipolar disorder (Hajek et al., 2019; Koutsouleris et al., 2014; Nenadic et al., 2017; Schnack et al., 2016), and first-episode psychosis (Kolenic et al., 2018), this study failed to find elevated BrainAGE scores in major depression on BrainAGE scores. While the initial study be Koutsouleris and colleagues did find elevated BrainAGE scores in MDD compared to healthy controls, a recent study in a healthy cohort analyzing effects of negative fateful life events also found an association of depressive symptoms with a similar indicator or brain aging (Hatton et al., 2018). Additional unpublished data in 211 MDD patients suggest a brain age gap of 0.8 years for MDD (Kaufmann et al.; pre-print at: https://www.biorxiv.org/content/biorxiv/early/2018/04/17/303164.full.pdf), and it also suggests that effect sizes might be rather low (in their study: Cohen's $d = 0.1$). It is worthwhile noting, that the BrainAGE indicator operates on a systems level and integrates data from voxels across the entire brain to derive a single metric for each individual. Hence, although being one single score, it intregrates a multi-variate information across the brain. It is therefore still possible that accelerated aging might occur in single regions (as opposed to multiple areas across the brain) as in schizophrenia or other disorders (Hajek et al., 2019; Kolenic et al., 2018; Nenadic et al., 2017; Schnack et al., 2016). Another methodological consideration to take into account is that the pre-processing with BrainAGE involves large learning samples and thus an age-related trajectory defining a standard norm, rather than diagnosis by age interaction analyses that have previously been used to index accelerated aging from cross-sectional MRI data (Nenadic et al., 2012; Sacchet et al., 2017). The BrainAGE score might, however, also be modulated by other factors such as obesity (Kolenic et al., 2018). Given that we did not include clinically obese patients or those with a manifest metabolic syndrome or uncontrolled diabetes, this is unlikely to have resulted in our negative findings, but might need consideration in future studies. However, other factors like oxidative stress or inflammation, which might also modulate age-related changes in MDD were not included in our study, so we could not test the hypothesis that these might mediate diagnosis-related differences. Similarly, psychiatric co-morbidities are unlikely to account for our findings, as they were absent in our MDD sample. Effects of antidepressant medication, as shown in previous imaging studies (Frodl et al., 2008), might add variance to regional brain volumes and thus impact on accuracy of BrainAGE or introduce bias; however, unlike antipsychotics, the direction of antidepressant-associated volume change is towards regional increase, so they would be expected to rather result in smaller BrainAGE score than false positives.

Our negative finding should also be considered in view of the clinical and neurobiological heterogeneity of major depression. For example, childhood maltreatment has been linked to variation in brain structure in MDD, modulating both the regional distribution of significant changes as well as effect magnitude (Opel et al., 2014; Teicher et al., 2018). Interestingly, childhood maltreatment, including physical neglect, might be a particular risk factor for aging-related molecular markers such as telomere length in MDD (Vincent et al., 2017). These might be associated with stress, thus leading to telomere changes which can be also detected in peripheral leukocyte (Wolkowitz et al., 2011). However, as a limitation of our study, we cannot infer on potential subgroups, given sample size as well as the limited knowledge on which biological processes and putative modulators might underlie accelerated aging in psychiatric disorders. The current literature on biological aging in major depression is limited with regards to the study of disease subtypes, as well as severity or chronicity.

Considering the hypothesis of accelerated brain aging on multiple biological levels, we might finally also consider molecular findings. There is indeed some evidence that some markers reflect systems-level changes while other are restricted to particular neural networks. For example, while telomere length-based indicators can be obtained from peripheral cells (leukocytes), there are also neuropathological studies of brain tissue, allowing differentiation of regional effects. Indeed, a recent post-mortem study investigating telomere length as a molecular marker of cellular aging showed regionally specific changes in the hippocampus of patients with MDD, but not amygdala, dorsolateral prefrontal cortex, nucleus accumbens, or substantia nigra (Mamdani et al., 2015). This would suggest regional specificity and argue against a global systems-level effect in the brain. It would thus be conceivable that such effects are expressed in singular brain regions rather than across the cortex or brain grey matter. However, post mortem studies themselves are limited in the choice of regions assessed, and therefore mostly cover selected regions of interest rather than the entire brain.

Additionally, genetic and epigenetic effects might substantially contribute on the impact that stressful life events might have on both symptoms and brain structural changes. Higher polygenic risk for depression and anxiety in a large female population was related to telomere shortening (Chang et al., 2018). Nikolova and colleagues noted that FREM3 related genetic variation in human subjects might be linked to risk for MDD as well as intermediate phenotypes such as amygdala activity and cognitive speed (Nikolova et al., 2015). Also, a large case-control study demonstrated that epigenetic markers of aging both in

peripheral and brain cells are related to clinical depression, and within the MDD patient group in particular with childhood trauma (Han et al., 2018). So far, it is not clear, how the observed telomere changes (either in blood or brain cells) are related to brain structural variation seen in MRI.

There are several limitations to consider in our study, and in particular the small sample size. This limits our ability to detect small to moderate effects, so the negative finding might have been a mere expression of lack of statistical power. Also, it is not clear how and whether co-morbidities affect accelerated aging in MDD. Given the selection in recruitment, our study is limited to a non-psychotic MDD phenotype without axis I or II co-morbidities. While this might give the advantage of limiting effects of other co-occurring conditions, we need to acknowledge that many MDD patients have co-morbid disorders. As with many other imaging markers, replication of studies is necessary, and despite the initial positive findings on MDD (Koutsouleris et al., 2014), there is a need for further replication and extension of findings as well as modifying factors. While our study therefore provides rather incremental advance, it provides an initial data set on a clinically selected pilot cohort, which fails to replicate the effects of larger samples (Koutsouleris et al., 2014) (Kaufmann et al.; pre-print at: https://www.biorxiv.org/content/biorxiv/early/2018/04/17/303164.full.pdf).

Altogether, the current emerging literature on accelerated aging in affective disorders lacks a conclusive evidence across the molecular, cellular, and network levels. In particular, there is a lack of studies in patients that would include both MRI based markers like BrainAGE to be combined with telomere length or other markers that might be available from blood samples.

5. Conclusion

In conclusion, our study failed to provide evidence for accelerated brain aging in a sample of MDD patients (without co-morbidities) as indicated by the BrainAGE score. However, further study in particular clinical subgroups is warranted to detect potential subtle changes, which might provide insights into systems-level brain aging related to clinical or genetic factors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.06.001.

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