Trajectory of brain maturation in young individuals at familial risk of mood disorder

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Abstract

Background:

Accelerated brain ageing has been proposed as a mechanism underlying mood disorder, but has been predominantly studied cross-sectionally in adult populations. It remains unclear whether differential ageing/maturation trajectories emerge earlier in life, in particular during the neurodevelopmental period of adolescence, and whether they are associated with onset of mood disorder and/or presence of familial risk.

Methods:

Participants included young individuals from the prospective longitudinal Scottish Bipolar Family Study (SBFS) with and without a close family history of mood disorder. All were well at time of recruitment. Implementing a structural MRI-based brain age prediction model, individual maturational trajectories were captured by the difference between predicted brain age and chronological age (brain-predicted age difference; brain-PAD) at baseline and at two-year follow-up. Based on follow-up clinical assessment, individuals were categorised into three groups: (i) controls who remained well (C-well, n=94), (ii) high familial risk who remained well (HR-well, n=73) and (iii) high familial risk who developed a mood disorder (HR-MD, n=38).

Results:

At baseline, brain-PAD was comparable between groups. However, we found negative trajectories of brain-PAD between baseline and follow-up for HR-MD versus C-well (β= -0.70 years, p<.001) and versus HR-well (β= -0.41 years, p=.01), and for HR-well versus C-well (β= -0.29 years, p=.05). Findings also provided modest evidence for maturational lags at two-year follow-up.

Conclusions:

These findings suggest that within young individuals, onset of mood disorder and familial risk may be associated with a deceleration in brain maturation trajectory. Extended longitudinal research will need to corroborate findings of emerging maturational lags in relation to mood disorder risk and onset.

Keywords: mood disorder, brain maturation, brain age prediction, structural MRI

Introduction

Mood disorders are amongst the most common psychiatric disorders, with a life-time prevalence of around 15% (Kessler and Bromet, 2013). Globally, they are the greatest contributor to non-fatal ill-health (World Health Organization, 2017). Although mood disorders are highly prevalent and disabling, underlying biological mechanisms remain unclear. However, it is known that mood disorders are highly heritable and share complex genetic architecture, for example individuals with a family history of Bipolar Disorder (BD) are at more than 10-fold greater risk of developing BD or Major Depressive Disorder (MDD) than the general population (Smoller and Finn, 2003). Mood disorders often manifest during adolescence and young adulthood (De Girolamo et al., 2012). These life stages involve great neurodevelopmental change, often referred to as brain maturation, as the organisation of brain structure contributes to cognitive development. But on the other hand these developmental stages also signify vulnerability to mental illness (Andersen, 2003; Dahl, 2004). However, to date previous research has mainly focused on mood disorders in adults with established illness using cross-sectional designs that are unable to address earlier origins of divergence. We were therefore interested in determining from longitudinal prospective data over the period of greatest risk for development of mood disorders, whether deviation of brain maturation in young individuals was related to concurrent mood disorder onset and/or to familial risk.

Parallel to other measures of biological ageing (e.g., epigenetic clock (Horvath, 2013)) a new framework for the investigation of brain maturation (from childhood to young adulthood) and ageing (from mid-adulthood) in relation to neuropsychiatry has emerged. This approach involves the estimation of an individual's "biological brain age" from an MRI scan, following the rationale that throughout life, the brain shows continual developmental trajectories of brain structure that shape cognition and behaviour. These trajectories are likely to show individual differences, that is, some individuals may be subject to faster or slower rates of structural changes in the brain associated with brain maturation or ageing. Certain deviations from normative brain developmental trajectories – in particular accelerated brain ageing, but potentially also differential brain maturation – have been found to be associated with psychopathology (Cole et al., 2019).

Researchers have developed and validated multiple methodologies to predict "biological brain age", most of which apply linear or non-linear regression methods to grey matter brain maps (for overview see: Cole et al., 2019). Specifically, Relevance Vector Regression (RVR) (Tipping, 2001) is

commonly implemented, and in one comparable study RVR with linear kernel showed the best performance for prediction of brain age, compared to various other regression methods (Franke et al., 2010). Subsequent to prediction, the “biological brain age” is compared to the individual’s chronological (brain) age, summarising the current status of brain development in a single measure: the brain-predicted age difference (brain-PAD) (Cole et al., 2019). Hereby, a larger brain-PAD in absolute terms indicates greater divergence from normative ageing; positive values reflect advanced brain maturation/ageing, and negative values reflect delayed brain maturation/ageing. Previous research in adult populations suggests that accelerated ageing, as reflected by brain-PAD, is predictive of mortality (Cole et al., 2018) and relates to diseases of older age such as dementia and to psychiatric conditions (for overview see: Cole et al., 2019). This approach therefore shows promise as a biomarker of brain development/maturation to investigate temporal origins of differences seen in adult mood disorder and its relationship to familial risk.

Development of mood disorder in young individuals could be reflected by accelerated brain maturation (positive brain-PAD), as an extension of theories of accelerated biological ageing in adults with MDD and BD (Rizzo et al., 2014; Wolkowitz et al., 2011). Indeed, biological mechanisms related to ageing, such as inflammation and oxidative stress, overlap with biological pathways implicated in mood disorders (discussed in: Sibille, 2013). Moreover, mood disorders have been associated with increased mortality rate (Ösby et al., 2001; Schulz et al., 2000) and age-related diseases such as type-II diabetes (Mezuk et al., 2008; Regenold et al., 2003) and coronary heart disease (Pan et al., 2011; Whooley et al., 2008). By implementing brain-PAD methods, Koutsouleris and colleagues (2014) found advanced ageing in adults with MDD (+4.0 years; *n* = 104, mean age = 42.2) and BD (+3.1 years; n = 57, mean age = 25.6) compared to healthy control participants (*n* = 43, mean age = 32.67). In contrast however, Nenadić and colleagues (2017) found no significant difference in brain ageing in smaller samples of adults with BD (*n* = 22, mean age = 37.7) versus healthy controls (*n* = 70, mean age = 33.8), highlighting the need for further research.

In contrast, given the complexity of biological brain changes associated with development and ageing across the lifespan, it may be that extending back mood disorder accelerated ageing theories to younger periods of brain development would be an over-simplification. In particular, within young individuals there is extensive re-organisation of the brain which (from late adolescence onwards) involves decreases in brain grey matter and fine-tuning/stabilisation of synapses, and that parallels

maturational changes in cognition and affect regulation (Giorgio et al., 2010; Spear, 2000). Here, it may be the case therefore that delayed maturation, rather than accelerated ageing, may be associated with vulnerability to psychiatric disorders. Phylogenetically older limbic areas are the earliest to mature, while maturation of higher-order cortical areas extends into young adulthood (Gogtay et al., 2004; Wierenga et al., 2016, 2014). Delayed brain maturation may therefore contribute to vulnerability to psychiatric disorders, particularly when such immaturity affects brain systems of cognitive control and emotional stability. One previous cross-sectional study (Hajek et al., 2017) implemented the brain-PAD framework to directly address this association between brain maturation and mood disorders in young adults, but found no significant differences in brain-PAD scores for those at familial risk and/or with a mood disorder.

As research to date has been primarily based on cross-sectional designs only, it remains unclear how the brain-predicted age difference may change over time and in relation to illness onset, emphasising the need for longitudinal investigations. It also remains unclear whether accelerated brain ageing in adults diagnosed with mood disorder should be viewed as a consequence of disease processes (argued by: James H. Cole et al., 2019), or if accelerated ageing also increases vulnerability to the development of mood disorder. Due to a lack of prospective longitudinal research in younger at-risk samples, the temporal origin of disease-related differences in brain ageing – and specifically whether they arise during adolescence or young adulthood – remains uncertain and could have important implications for intervention (both targeted prevention and treatment).

To address this significant gap in research, the current study investigated divergence of normative maturational trajectories in young individuals by applying the brain-PAD framework within a prospective longitudinal design, starting before mood disorder onset. Specifically, we used data from the Scottish Bipolar Family Study (SBFS), which included young individuals who were all initially well and some of whom had a close family history of BD. The longitudinal character of the study enabled the investigation of brain-PAD over two years, to assess differences in dynamic brain maturation trajectories for those who were at high risk for mood disorder and/or subsequently developed illness. As all individuals were initially well, an increase in brain-PAD would suggest that accelerated brain maturation (in case of positive trajectory of brain-PAD) or decelerated brain maturation (in case of negative trajectory of brain-PAD) might play a causal role in mood disorder onset, potentially by increasing vulnerability to disease.

Recognising similarities between BD and MDD in symptomatology and genetic architecture, as well as the difficulty of defining a definitive stable diagnosis at young age, early-onset mood disorder was defined as having an onset of MDD or BD during adolescence or young adulthood. We predicted that the development of early-onset mood disorder would be associated with divergent brain maturation trajectories. Due to lack of direct empirical evidence, we considered that this could manifest as either acceleration or deceleration in brain maturation. Furthermore, we hypothesised that the presence of positive familial risk would also be associated with differences in brain-PAD at baseline and follow-up.

Methods

Participants

Participants were adolescents and young adults (N = 284, age 16-25 years) recruited as part of the Scottish Bipolar Family Study (SBFS) (Chan et al., 2016; Ganzola et al., 2018; Sprooten et al., 2011; Whalley et al., 2015). Participants at high familial risk of mood disorder (HR-participants) had at least one first-degree relative or two second-degree relatives with BD type-I, and were thus at increased risk of developing a mood disorder (i.e., over 10-fold increased risk for both BD and MDD) (Smoller and Finn, 2003). Unrelated control participants without family history of BD or other mood disorder were recruited from the social networks of HR-participants, and were matched to the HR-group by age and sex. Further details of familial structure within the groups are described in Supplementary Methods 1 (see Supplementary Materials). Exclusion criteria ensured that, at the time of recruitment, all participants had no personal history of MDD, mania or hypomania, psychosis, or any other major neurological or psychiatric disorder, substance dependence, learning disability, or head injury that included loss of consciousness, and that they were without contraindications to MRI. Therefore, all individuals (HR and control) were considered well at the baseline imaging assessment.

The following additional exclusion criteria were applied in the context of the current study: (i) missing MRI or age data (n = 40), (ii) scans of insufficient image or segmentation quality (n = 14; for details see Supplementary Methods 3), (iii) unclear or other psychiatric diagnosis without mood disorder (n = 4), and (iv) high familial risk for mood disorder without follow-up measurement (n = 9). These criteria excluded 67 participants, reducing the sample size to a total of 217 participants at

timepoint 1 (111 HR-participants), with follow-up timepoint 2 data available for 136 of these participants (80 HR-participants).

Procedure

Participants of the SBFS were invited every two years for a total of four assessments over six years (Whalley et al., 2015). Participants were interviewed and screened with the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID) (First et al., 2002) by two trained psychiatrists at timepoint 1 to ensure that they were all initially well, and at timepoint 2 to determine the presence of any mood disorder meeting diagnostic criteria since the previous assessment. Timepoint 2 clinical information was available for 93% of the included control participants, and for all included HR-participants. Participants were categorised as well or diagnosed with mood disorder accordingly. Individuals with well outcomes at the earlier two assessments were assumed to have remained well in the absence of further clinical information to the contrary at timepoint 3 (see Supplementary Materials, Table S1). Additionally however, if individuals were subsequently found to have been diagnosed with mood disorder at further assessments (*n* = 15; either through face-to-face assessments or through accessing clinical records at National Health Service (NHS)), they were then categorised in the mood disorder group. Including these participants in the mood disorder group enables the investigation of early (and potentially causal) disease mechanisms, while keeping the well-groups as pure as possible. This method of group categorisation has been succesfully applied in previous research (Chan et al., 2016). Group categorisation resulted in the following groups: control participants who remained well (C-well, *n* = 94), HR-participants who remained well (HR-well, *n* = 73), and HR-participants who developed a mood disorder (HR-MD, *n* = 38, including 6 BD). As only a small number of control participants developed a mood disorder (*n* = 12, including 2 BD), these participants were not included in the main analysis (see Supplemental Results 3).

The National Adult Reading Test (NART) (Nelson and Willison, 1991) and Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) were administered at the time of scanning. The participant's age at the time of each assessment was registered in years with a precision of two decimals. Assessments at timepoint 1, timepoint 2 and timepoint 4 included an MRI session, although only MRI measurements at timepoint 1 and timepoint 2 were considered within this study to restrict to a single scanner. The SBFS was approved by the Research Ethics Committee for Scotland, and

written informed consent including consent for data linkage via medical health records was acquired from all participants.

MRI acquisition and pre-processing

Timepoint 1 and timepoint 2 MRI sessions were carried out on a 1.5 T Signa scanner (GE Medical, Milwaukee, USA) at the Brain Research Imaging Centre in Edinburgh and included a structural T1 weighted sequence (180 contiguous 1.2 mm coronal slices; matrix = 192 x 192; fov = 24 cm; flip angle 8°).

Pre-processing of T1 weighted scans was done in Statistical Parametric Mapping (SPM) version 12. The Computational Anatomy Toolbox (CAT) toolbox (version CAT12.3 (r1318); Gaser and Dahnke, 2018), which runs on SPM12 software, was used to segment T1-weighted MRI scans into different tissue types (for details on CAT12, see Supplementary Methods 3). Subsequently, modulated grey matter maps (GMM) were smoothed with a Gaussian kernel (FWHM = 8 mm). After loading the smoothed GMM (sGMM) into Python version 3.5.4, voxels were resampled into voxels of double the original voxel size, i.e. 3 x 3 x 3 $mm^{3.}$ This reduced the number of voxels without further loss of spatial information. The sGMM were then masked with a threshold of 0.01 to ensure that voxels outside the brain were represented by value zero. The resulting sGMM were used as input for the brain-PAD model.

Brain-PAD model

To initially train the brain age prediction model, the training sample included all control and HR-participants that remained well (n = 167) in order to maximise the healthy sample size (a model including control participants only was considered underpowered, see Supplementary Methods 4). In order to account for the follow-up assessment timepoint, the current model was equally balanced across timepoint 1 and timepoint 2 measurements in such way that the age range of the training sample was maximal (M = 22.35, SD = 2.96, range = 15.2-28.1 years). Similar to previous studies (reviewed by: Cole et al., 2019), the sGMM and corresponding chronological ages of the training sample were used to train a brain age prediction model. Corresponding to recent recommendations (Smith et al., 2019), this model initially consisted of reduction of features (i.e., all sGMM voxels) to 73 brain components (based on eigenvalue > 1) with use of principal component analysis (PCA) based

on singular value decomposition (scikit-learn PCA). Using these brain components as input we subsequently estimated an RVR model with linear kernel to achieve brain age prediction. The trained model was then applied to each participant's sGMM to predict their brain age, ensuring that the participant for whom the brain age was being predicted was left out of the training sample to prevent bias (leave-one-out training). A residuals approach including sex as covariate to account for sex differences was used to calculate brain-PAD (for details see Supplementary Methods 5), i.e. the gap between brain age prediction and chronological age. This residuals based approach is typically used to derive measures of accelerated ageing (e.g. epigenetic ageing; Chen et al., 2016; Horvath, 2013) and is recommended for brain-PAD approach (Smith et al., 2019). Regarding brain development, a positive brain-PAD reflected a brain-predicted age older than the chronological age of the participant, while a negative brain-PAD indicated a brain-predicted age younger than the participant's chronological age. Changes in brain-PAD over time indicated a relative acceleration in brain maturation if brain-PAD became more positive (or less negative), or a relative deceleration in brain maturation if brain-PAD became more negative (or less positive). Due to the rarity of such prospective data of young individuals (including adolescents), no independent dataset was available for optimal evaluation of the brain-PAD model. Hence the model was evaluated based on the brain age predictions for the training sample (leave-one-out cross-validation).

Comparison of brain maturation trajectories

Since the objective of this study was to investigate deviation of brain maturation trajectories in young individuals at high risk for mood disorder and the association with illness onset, participants were divided in three groups based on clinical information as described above. Clinical information from all available assessments was considered in group categorisation as described above.

As main analysis, a linear mixed model was applied to the brain-PAD measures in order to compare brain maturation trajectories between groups (Gueorguieva and Krystal, 2004), with C-well as reference group. The random term was defined as family identity with subject identity nested within it. This analysis was also repeated after re-referencing groups to HR-well, enabling comparison of the two HR groups. To facilitate a comparison with previous cross-sectional findings, we additionally explored group differences in average brain-PAD at timepoint 2 with two linear mixed models that only considered timepoint 2 and excluded the time interaction effect, referenced by C-well and HR-well

respectively. Furthermore, a supplementary analysis also included the group of control participants who developed a mood disorder (C-MD).

Results

Demographics

Sample sizes, demographic information and clinical measures are presented in Table 1. There were no significant differences between groups with regard to age at either timepoint, and no differences in gender, handedness and NART intelligence quotient score. Depressive symptom severity as measured by HRSD significantly differed between groups. At both timepoints, greater depression symptomatology was observed for HR-MD as compared to the groups of participants who remained well (C-well and HR-well).

Model evaluation

Brain age predictions and chronological age had significant positive Pearson correlation within the training sample ($r(165) = .36$, $p < .001$), while mean absolute prediction error was 2.26 years. With lower correlation but higher precision of the brain age prediction as compared to previous studies (likely to be related to the more specific age range of the current sample), these model evaluation results are considered to be acceptable for the aim of the current study (for a discussion see Supplementary Results 1). Exploration of the 73 brain components (that were used as input for the brain age prediction algorithm) indicated an explained variance of 84% within the training sample (see Figure S2 in Supplemental Materials).

Comparison of brain maturation trajectories

Comparison at baseline. Group allocation based on diagnostic information resulted in mean brain-PADs of +0.01 (*SD* = 1.21, *n* =) for C-well, -0.33 (*SD* = 1.18, *n* =) for HR-well, and -0.00 (*SD* = 1.37, *n* =) for HR-MD. There was a non-significant trend of a small delay at baseline for the comparison of HR-well versus C-well ($\beta = -0.38$, $p = 0.06$) (Table 2). We found no baseline differences in brain-PADs for HR-MD when compared to C-well ($\beta = -0.07$, $p = 0.75$) or between HR-well and HR-MD ($\beta = -0.31$, $p = 0.22$),

Brain maturation trajectories. Results showed a significant timepoint*group interaction effect for HR-MD (β = -0.70 years, p <.001) and to a lesser degree for HR-well (β = -0.29 years, p = .05), indicating deceleration in brain maturation in comparison to the C-well group. There was also showed a significant timepoint*group interaction effect for HR-MD versus HR-well (β = -0.41 years, p = .01). Figure 1 displays brain maturation trajectories per group as modelled by the fixed effects, for clarity corrected for the effects observed in C-well (i.e., intercept and the significant timepoint coefficient, see Table 2). Figure 2 shows the heterogeneity in 'raw' (unmodelled and uncorrected) brain maturation trajectories by displaying the participants' individual changes in brain-PAD over time.

Comparison at follow-up. At follow-up, two years later, the mean brain-PADs were +0.35 (*SD* = 1.08) for C-well, -0.06 (*SD* = 1.10) for HR-well, and -0.28 (*SD* = 1.27) for HR-MD. Comparisons at follow-up indicated a significant difference in brain-PAD between HR-MD and C-well (β = -0.67, p = .02), and a non-significant trend for HR-well versus C-well (β =- 0.47, p = .07), but the additional model showed no evidence for a difference between HR-MD and HR-well at follow-up (β = -20, p = 0.46).

Discussion

The results of the current study showed that in young individuals, differential brain developmental trajectories as investigated with brain-PAD were associated with the development of mood disorder and familial risk. Significant increases in negative brain-PAD between baseline and follow-up showed that brain maturation decelerated in young individuals who were at familial risk and developed a mood disorder, and to a lesser degree, such deceleration was also found in those who were at familial risk but remained well. Importantly, all participating young individuals were initially well and with comparable status of brain maturation (although we found a small non-significant baseline delay in brain maturation within HR participants who remained well). Since group categorisation and comparison was based on subsequent clinical assessment, the findings of the present study indicated that the emergence of a maturational lag during adolescence and young adulthood may be related to familial risk and prodromal or early stages of mood disorder psychopathology. The findings also provided some modest evidence of a delay in brain maturation at two-year follow-up within all young individuals at risk (regardless of mood disorder status). It is important to note however that all groups showed considerable heterogeneity in the direction, size and emergence of the individual brain-PADs. Therefore, additional research supporting the current study results is required to substantiate the

hypothesis of the emergence of maturational lag being related to youth mood disorder onset and familial risk.

As cognitive functions develop as a result of brain maturation, deceleration in brain maturation may potentially generate an imbalance in the brain that delays development of effective emotion regulation and cognitive control. Previous longitudinal research suggests that impairments in emotion regulation and cognitive control are associated with subsequent increase in depressive symptoms (Aldao et al., 2010). Many models of psychopathology therefore propose that ineffective emotion regulation and impaired cognitive control play a causal role in the development of mood disorder (e.g., Nolen-Hoeksema et al., 2008; Phillips et al., 2008). Corresponding to this view, deceleration in brain maturation during adolescence and young adulthood is hypothesised to increase vulnerability to mood disorder through underdevelopment of emotion regulation and cognitive control brain functions.

Importantly, our findings suggest that disease-related differences in maturational trajectory may emerge during adolescence and young adulthood, but if so, that the direction of this difference is opposite to findings of accelerated ageing in older adults diagnosed with mood disorder (Koutsouleris et al., 2014; Sibille, 2013; Wolkowitz et al., 2011). Deceleration in brain maturation can be reconciled with adult accelerated brain ageing in two ways, which are not mutually exclusive. Firstly, since non-linear developmental and ageing trajectories in the brain have been well-established (Giedd et al., 1999; Scahill et al., 2003; Shaw et al., 2008; Tamnes et al., 2010; Wierenga et al., 2014), a linear divergence in the brain-predicted age difference (brain-PAD) across the life-course and in relation to disease is unlikely. Other measures of biological ageing, such as epigenetic ageing measures, suggest that biological ageing/maturational trajectories across the life-course are also not linear (Boks et al., 2015; Christiansen et al., 2016). As it has been proposed that accelerated ageing is a consequence of mood disorder disease processes, a positive brain-PAD indicating advanced ageing may emerge later in life. However, further research is needed to determine when the turning point from decelerated to accelerated ageing takes place, and if it is distinctive to the development of mood disorder. Secondly, the hypothesis that decelerated brain maturation in adolescence or young adulthood may have a causal influence on the development of mood disorder through suboptimal cognitive and emotional functioning may extend to adulthood. Since cognitive functions decline with ageing, the disadvantage of accelerated ageing in adulthood could be viewed as being in parallel with

decelerated brain maturation during adolescence and young adulthood; possibly, suboptimal functioning of the brain puts an individual at risk for the development of mood disorder.

The current study applied a novel method that, to our knowledge, has not been previously implemented in a longitudinal cohort study of young individuals at familial risk of mood disorders. Collecting clinical data from larger youth cohorts is difficult and such datasets are therefore sparse; hence, the SBFS provided a unique opportunity to investigate the dynamics of brain maturation trajectories in relation to mood disorder, enabling important insights into the prediction of mood disorder onset in young individuals. Development of mood disorder was found to be associated with decelerated brain maturation, which could not have been identified within a cross-sectional design. Furthermore, clinical information extended this two-year period, as it was available for up to six years depending on continuation of study participation (for details see Supplementary Methods 2). It is also important to note that extended follow-up could have contributed to heterogeneity within the mood disorder groups, as some individuals had already experienced mood disorder onset at follow-up while others would only have experienced it years later. Overall, by using data from the SBFS, the current study shows unique strengths for mental health research in young individuals. Ongoing work on the sample seeks to implement data linkage at 10+ years to obtain more definitive, stable diagnoses.

One of the limitations of our study is in the sample size, and consequently, suboptimal performance of the brain age prediction model. Also because of the importance of training sample size in relation to robust model development, the model was trained on all individuals who remained well including those at high familial risk for mood disorder, which could obscure differences related to familial risk. Brain-PAD slightly increased over time within the control group, indicating the emergence of a small difference between brain-predicted age and chronological age, and reflecting that a brain-PAD of zero did not indicate normative brain maturation in the current study. However, this bias is unlikely to affect the investigation of the relative differences in brain-PAD between groups. Furthermore, it is important to note that due to the rarity of the sample it was not possible to validate our brain-PAD model within an independent young cohort. Constrained by what is achievable with the current sample sizes, we directly addressed these limitations to the best of our abilities (by application of a residuals approach, dimensionality reduction and sparse modelling via RVR) in an attempt to prevent overfitting and optimise the overall validity of the model.

Future research should aim to replicate the current results within a larger sample and with

longer follow-up in order to fully tackle the above limitations, enhance the performance of the brain age prediction model, and yield more reliable results for all group comparisons (Button et al., 2013). This would also allow for investigation of similarities and differences between MDD and BD by considering these disorders separately, and by taking into account potential medication effects, should group numbers be sufficient. Additionally, with increased sample sizes, brain-PAD model interpretability can be enhanced by application of orthonormal projective non-negative matrix factorisation (OPNMF) of grey matter (Sotiras et al., 2015; Varikuti et al., 2018), as this method produces model components that represent biologically meaningful clusters within the brain (Sotiras et al., 2017). This method can address whether brain regions involved in networks for emotion regulation and cognitive control are influential in brain age prediction for young individuals, and investigate local differences in brain maturation associated with the development of mood disorder. For now, the present study lays a theoretical and empirical foundation for the field to build upon and will hopefully encourage researchers to further undertake extensive longitudinal clinical cohort studies in youth, enabling replication and more thorough investigation of the suggested link between decelerated brain maturation and mood disorders in youth.

Supporting information

Supplementary Materials can be found in the online version of this article.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of

the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Tables and figures

Table 1. Demographic and clinical characteristics.

	C-well	**HR-well**	**HR-MD**	***p*-value**
n, timepoint 1	94	73	38	
n, timepoint 2	47	48	32	
Age, timepoint 1[a]	21.6 (3.8)	21.6 (5.0)	21.4 (5.2)	.80
Age, timepoint 2[a]	23.4 (3.8)	23.7 (5.1)	23.4 (5.0)	.45
Gender[b]				.66
Male	43 (45.7%)	37 (50.6%)	16 (42.1%)	
Female	51 (54.3%)	36 (49.4%)	22 (57.9%)	
Handedness[b]				.81
Left	5 (5.3%)	7 (9.6%)	2 (5.3%)	
Right	86 (91.5%)	65 (89.0%)	36 (94.7%)	
Mixed	1 (1.1%)	1 (1.4%)	0 (0%)	
Unknown	2 (2.1%)	0 (0%)	0 (0%)	
NART score[a]	111 (9.2)	111 (10.8)	107 (8.6)	.29
HRSD, timepoint 1[a]	0 (1.0)	0 (2.0)	2 (5.3)	<.001*** [α]
HRSD, timepoint 2[a]	0 (2.0)	0 (1.0)	4 (7.3)	<.001*** [α]

*** *p < .001*

Note: Individual NART scores were averaged over all completed assessments (max. 4).

[a] Medians and interquartiles for variables not normally distributed (Kruskal-Wallis test)

[b] Frequency and percentages for categorical variables (chi-squared).

[α] HR-MD vs. C-well and HR-well.

C-well, group of participants without family history who remained well; HR-MD, group of participants at high familial risk who developed a mood disorder; HRSD, Hamilton Rating Scale for Depression; HR-well, group of participants at high familial risk who remained well; NART, National Adult Reading Test.

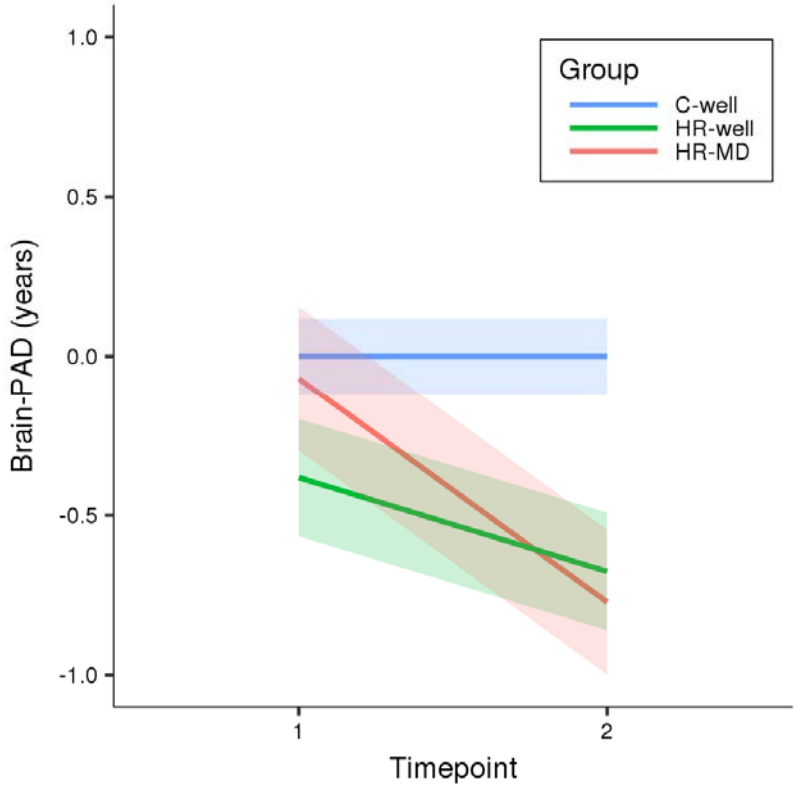

Figure 1. Modelled fixed effects of the brain-predicted age difference (brain-PAD) per group, for clarity corrected for effects in C-well (i.e., the intercept and timepoint coefficients) as this group functions as control and reference group within the main analysis. Shaded areas display standard errors of the timepoint fixed effects per group.

Brain-PAD, brain-predicted age difference; C-well, group of participants without family history who remained well; HR-MD, group of participants at high familial risk who developed a mood disorder; HR-well, group of participants at high familial risk who remained well.

Table 2. Fixed effects of linear model applied to investigate group differences in the brain-predicted age difference (brain-PAD).

Main model (references C-well)					
Fixed effect	***β*-coefficient**	***SE***	***df***	**t-value**	***p*-value**
(Intercept)	-0.04	0.12	176	0.14	.89
Timepoint 2	0.44	0.10	124	4.27	<.001***
HR-well	-0.38	0.15	26	-2.00	.06
HR-MD	-0.07	0.24	26	-0.32	.75
Timepoint 2*HR-well	-0.29	0.13	124	-2.02	.05*
Timepoint 2*HR-MD	-0.70	0.16	124	-4.29	<.001***
Additional model (references HR-well)					
Fixed effect	***β*-coefficient**	***SE***	***df***	**t-value**	***p*-value**
HR-MD	0.31	0.24	26	1.27	.22
Timepoint 2*HR-MD	-0.41	0.16	124	-2.49	.01*

** p < .05, ** p < .01, *** < .001*

C-well, group of participants without family history who remained well; HR-MD, group of participants at high familial risk who developed a mood disorder; HR-well, group of participants at high familial risk who remained well.

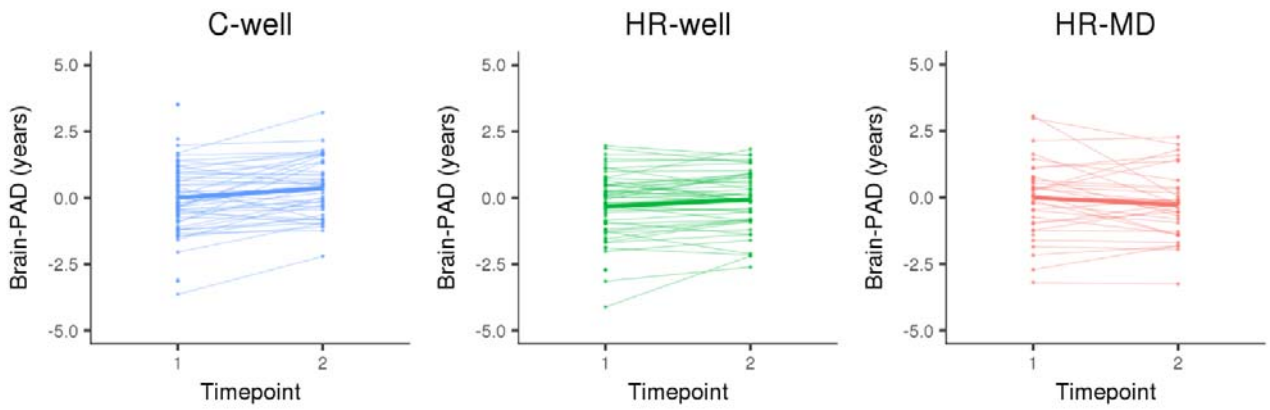

Figure 2. Display of brain maturation trajectories per participant. Brain maturation trajectory is reflected by a changing brain-predicted age difference (brain-PAD) between timepoint 1 and timepoint 2, two years apart. Each panel contains the brain maturation trajectories of one group in thin line graphs, whereas the thicker line graph represents the average maturation trajectory of that group. Left panel, C-well; Middle panel, HR-well; Right panel, HR-MD.

Brain-PAD, brain-predicted age difference; C-well, group of participants without family history who remained well; HR-MD, group of participants at high familial risk who developed a mood disorder; HR-well, group of participants at high familial risk who remained well.