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

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Abbreviated title: Adolescent brain maturation and mood disorders

Abstract

Background:

Accelerated biological 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 were young individuals (16-25 years) from the prospective longitudinal Scottish Bipolar Family Study (SBFS) with and without 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-PAD) at baseline and two-year follow-up. Based on clinical assessment at follow-up, 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:

Results showed no differences in brain-PAD between groups at baseline or follow-up. However, we found negative trajectories of brain-PAD for HR-MD versus C-well (β= -0.68 years, p<.001) and versus HR-well (β= -0.38 years, p=.01), and for HR-well versus C-well (β= -0.30 years, p=.03).

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. However, without significantly differential status of brain maturation at follow-up, extended longitudinal research will need to show whether this marks the emergence of maturational lag.

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 & 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: individuals with a family history of Bipolar Disorder (BD) are at risk of developing both BD and Major Depressive Disorder (MDD) (Smoller & Finn, 2003). Mood disorders often manifest earlier in life during adolescence (de Girolamo *et al.*, 2012), a period that involves great neurodevelopmental change (e.g., Wierenga *et al*. 2016). The neurodevelopmental change continues into young adulthood and is often referred to as brain maturation, as the organisation of brain structure contributes to cognitive development. Adolescence is therefore considered to be a period of significant vulnerability to mental illness (Andersen, 2003; Dahl, 2004). However, 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 whether deviation of brain maturation during the adolescent period is related to mood disorder onset in young adulthood, and to familial risk (the largest known risk factor for mood disorders).

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 adolescent brain maturation – are found to be associated with psychopathology (for overview see: Cole *et al.*, 2018).

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.*, 2018). 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.*, 2018). Hereby, a larger brain-PAD in absolute terms indicates greater divergence from normative ageing, reflecting advanced brain maturation/ageing if positive but a delayed brain maturation/ageing if negative.

Development of mood disorder in adolescence could be reflected by accelerated brain maturation, as an extension of accelerated ageing in adults diagnosed with MDD (Wolkowitz *et al.*, 2011) and BD (Rizzo *et al.*, 2014). Biological mechanisms related to ageing, such as inflammation and oxidative stress, overlap with biological pathways implicated in mood disorders (see Sibille, 2013). Moreover, mood disorders have been associated with age-related diseases, such as type II diabetes (Regenold *et al.*, 2003; Mezuk *et al.*, 2008) and coronary heart disease (Whooley *et al.*, 2008; Pan *et al.*, 2011), and with increased mortality rate (Schulz *et al.*, 2000; Ösby *et al.*, 2001). By implementing brain-PAD methods, Koutsouleris *et al.* (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, Nenadić *et al.* (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).

Taken together, however, previous research suggests that accelerated biological ageing in adults diagnosed with mood disorder may also extend to ageing of the brain. If so, it remains unclear whether accelerated brain ageing in adults diagnosed with mood disorder should solely be viewed as a consequence of disease processes (Cole *et al.*, 2018), or if accelerated ageing also increases vulnerability to the development of mood disorder. Due to a lack of longitudinal research in younger samples, the temporal origin of disease-related differences in brain ageing – and specifically whether they arise during adolescence – remains uncertain and could have important implications for intervention (both targeted prevention and treatment).

During adolescence, however, there is extensive re-organisation of the brain, paralleling maturational changes in cognition and affect regulation (Spear, 2000; Giorgio *et al.*, 2010). This predominantly involves the fine-tuning and stabilisation of synapses. Phylogenetically older limbic

areas are the earliest to mature, and higher-order cortical areas are amongst the latest (Gogtay *et al*., 2004, Wierenga *et al.*, 2014; Wierenga *et al.*, 2016). It is hypothesised this maturational mismatch during adolescence could contribute to vulnerability to psychiatric disorders. Alternatively, therefore, divergence could manifest as delayed rather than accelerated brain maturation, reflecting immaturity of cognitive systems and resultant emotional instability and disease vulnerability characteristic of this period. One previous study has implemented the brain-PAD framework to directly address the association between adolescent brain maturation and mood disorders (Hajek *et al*., 2017). This cross-sectional study however found no significant differences in brain-PAD scores between young subjects at familial risk with a mood disorder (n = 48, mean age = 23.1), versus those at familial risk who were well (n = 48, mean age = 20.9), and control subjects (n = 60).

As previous research was 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. To address this significant gap in research, the current study investigated divergence of normative maturational trajectories in adolescence 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 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 adolescent brain maturation (in case of positive brain-PAD) or decelerated adolescent brain maturation (in case of negative 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 in adolescence or young adulthood of MDD or BD. 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; Sprooten *et al.*, 2011; Whalley *et al*., 2015; Papmeyer *et al*., 2015; Chan *et al.*, 2016; Ganzola *et al*., 2018). Participants at high familial risk of mood disorder (HR-participants) have at least one first-degree relative or two second-degree relatives with BD type-I, and are thus at increased risk of developing a mood disorder (both BD and MDD; Smoller & 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 shown in the 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; see supplementary materials for details), (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 (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, but are presented in the supplementary materials for completeness (see below).

The National Adult Reading Test (NART) and Hamilton Rating Scale for Depression (HRSD) 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 carriedf 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 (see supplementary materials for details) yielded smoothed grey matter maps (sGMM), which were used as input for the brain-PAD model.

Brain-PAD model

The training sample – for training of the brain age prediction model – was based on all control participants and HR-participants that remained well (*n* = 167) in order to maximise the sample size (a model just including control participants was underpowered, and consequently invalid, see supplementary materials for details). In order to improve follow-up age predictions, the current model was also 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). Corresponding to some of the previous studies (reviewed by Cole et al., 2018), sGMM and corresponding chronological ages of the training sample were used to train a brain age prediction model that consisted of reduction of features (i.e., sGMM voxels) with principal component analysis (PCA) to 73 components (based on the Kaiser criterion), followed by estimation of an RVR model with a linear kernel. The trained model was 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 gender as covariate to account for sex differences was used to calculate brain-PAD (see supplementary materials for details), i.e. the gap between brain age prediction and chronological age. This approach takes the residuals of regressing brain age prediction on chronological age within the training sample and is typically used to derive other measures of accelerated ageing, for example in the field of epigenetic ageing (Horvath, 2013; Chen *et al.*, 2016). Regarding adolescent 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 adolescent data, 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 adolescents who were at high risk for mood disorder and/or developed illness, 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 & 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 three Welch independent t-tests. 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 ($r(165) = .37$, $p < .001$), while mean absolute prediction error was 2.25 years. This is considered acceptable for comparisons of brain age predictions between groups (see supplementary materials for discussion).

Comparison of brain maturation trajectories

Comparison at baseline. Group allocation based on diagnostic information resulted in mean brain-PADs of -0.03 (*SD* = 1.19) for C-well, -0.34 (*SD* = 1.18) for HR-well, and -0.02 (*SD* = 1.22) for HR-MD. The fixed effects of the model (Table 2) showed no baseline differences in brain-PADs for

HR-well or HR-MD when compared to C-well in the main analysis, nor for HR-well versus HR-MD in the additional analysis.

Brain maturation trajectories. Importantly, results showed a significant timepoint*group interaction effect for HR-MD (β = -0.68 years, p <.001) and to a lesser degree for HR-well (β = -0.30 years, p = .02), indicating deceleration in brain maturation of -0.68 years and -0.30 years on average, respectively, in comparison to C-well. The additional analysis re-referenced by HR-well also showed a significant timepoint*group interaction effect for HR-MD (β = -0.38 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 +0.30 (SD = 1.05) for C-well, -0.10 (SD = 1.04) for HR-well, and -0.23 (SD = 1.25) for HR-MD. Comparisons at follow-up indicated no significant differences in brain-PAD between C-well and HR-well (t(92.9) = 1.83, p = .07), nor between C-well and HR-MD (t(59.3) = 1.95, p = .06).

Supplementary analysis. The results of the analysis including C-MD in the model showed a similar trend of deceleration in brain maturation for this group (see supplementary materials, Table S2 and Figure S2).

Discussion

The results of the current study showed that in adolescent individuals, differential brain developmental trajectories, as investigated with brain-PAD, were associated with the development of mood disorder and familial risk. It is important to note however that all groups showed considerable heterogeneity in the direction, size and emergence of the individual brain-PADs. Specifically, results indicated no significant group differences in brain maturation associated with familial risk or illness at baseline, nor at follow-up. However, a significant increase in negative brain-PAD between baseline and follow-up showed that adolescent brain maturation decelerated in 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. Although cross-sectionally the delay in brain maturation at two-year follow-up was not significant for either high risk group (relative to the control

group), the deceleration in brain maturation potentially indicates the emergence of a maturational lag. Since all individuals were well at baseline (with group categorisation based on subsequent clinical assessments), our findings suggest that decelerated adolescent brain maturation may be related to prodromal and early stages of mood disorder psychopathology, as well as familial risk for mood disorder. Additional research supporting the current study results is required to substantiate this hypothesis.

As cognitive functions develop as a result of adolescent brain maturation, deceleration in adolescent 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., Phillips *et al.*, 2008; Nolen-Hoeksema *et al.*, 2008). Corresponding to this view, deceleration in adolescent brain maturation 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, but if so, that the direction of this difference is opposite to findings of accelerated ageing in adults diagnosed with mood disorder (Wolkowitz *et al.*, 2011; Sibille, 2013; Koutsouleris *et al.*, 2014). Deceleration in adolescent 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, 2016), 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*., 2015). 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 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; possibly, suboptimal functioning of the brain puts an individual at risk for the development of mood disorder.

Although adolescence is viewed as a period of vulnerability to psychopathology, prospective longitudinal imaging data on adolescent mental health is only scarcely available; hence, the SBFS provided a unique opportunity to investigate the dynamics of adolescent brain maturation trajectories in relation to mood disorder. 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 (see supplementary materials for details). Although not available for all participants, extended clinical follow-up where available is desirable for reliable group categorisation. Some individuals in the well-groups who discontinued study participation may have subsequently become unwell; we note however that around 3/4 of the HR-well individuals did have follow-up data until timepoint 3, and that if any participant who was assumed to have remained well later on developed illness, this would most likely mean that our results would be diluted rather than erroneous. 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 adolescent mental health research. 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 adolescent 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 (Soritas *et al.*, 2015, Varikuti *et al.*, 2018), as this method produces model components that represent biologically meaningful clusters within the brain (Soritas *et al.*, 2017). This method can address whether brain regions involved in networks for emotion regulation and cognitive control are influential in adolescent brain age prediction, and investigate local differences in brain maturation associated with the development of mood disorder.

Conclusions

With implementation of the brain-predicted age difference (brain-PAD) framework within a prospective longitudinal study with high-risk design, we were able to show differential adolescent brain maturation dependent on family history of BD and with the subsequent development of mood disorder. Specifically, adolescent brain maturation was found to decelerate in young individuals who were at familial risk for mood disorder, and this deceleration was largest in the group of individuals who developed a mood disorder. Although ‘status of brain maturation’ did not significantly differ between groups at follow-up, the deviating slope of brain maturation over time may indicate the emergence of a brain maturational lag in young individuals who are in prodromal or early stages of mood disorder psychopathology. Further longitudinal research will be required to unravel the relationship between

differential adolescent brain maturation and mood disorders – research that includes an even more substantial sample of adolescents and that extends the current two-year follow-up period.

Supporting information

Additional Supporting Information may 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).

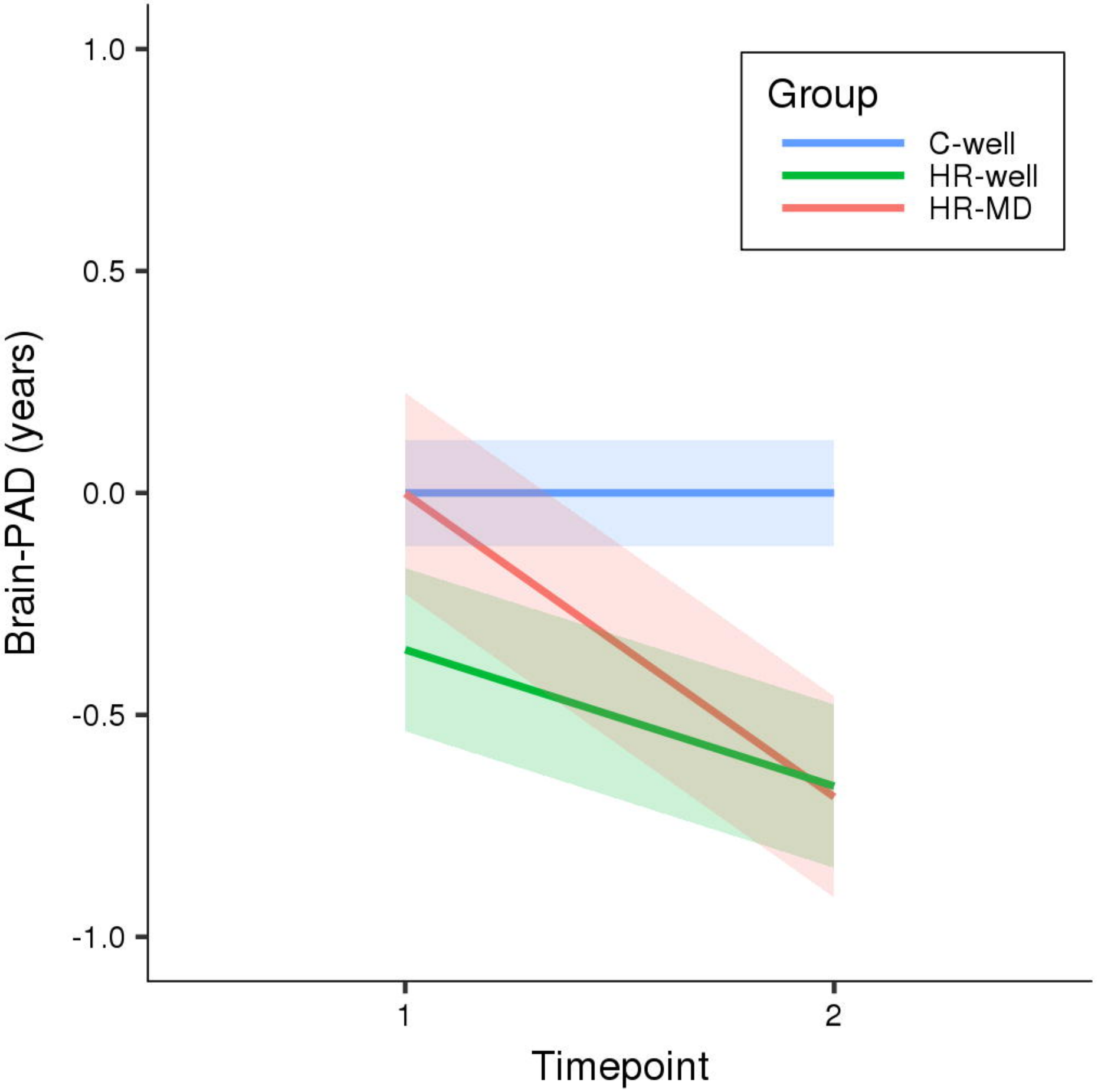
Main model (references C-well)					
Fixed effect	***β*-coefficient**	***SE***	***df***	**t-value**	***p*-value**
(Intercept)	-0.04	0.12	202	-0.29	.78
Timepoint 2	0.44	0.09	124	4.62	<.001***
HR-well	-0.31	0.18	202	-1.68	.09
HR-MD	0.06	0.22	202	0.26	.79
Timepoint 2*HR-well	-0.30	0.13	124	-2.24	.03*
Timepoint 2*HR-MD	-0.68	0.15	124	-4.54	<.001***
Additional model (references HR-well)					
Fixed effect	***β*-coefficient**	***SE***	***df***	**t-value**	***p*-value**
HR-MD	0.35	0.24	26	1.49	.15
Timepoint 2*HR-MD	-0.38	0.15	124	-2.52	.01*

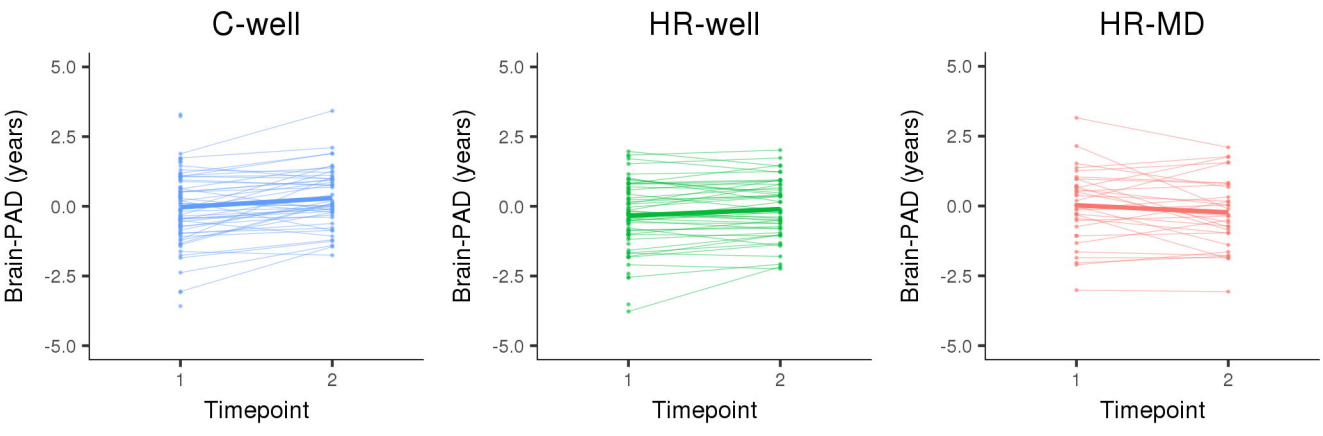
** p < .05, ** p < .01, *** < .001*

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.


Group
C-well
HR-well
HR-MD
1.0
0.5
0.0
-0.5
-1.0
Brain-PAD (years)
1
2
Timepoint


C-well
HR-well
HR-MD
Brain-PAD (years)
5.0
2.5
0.0
-2.5
-5.0
1
2
Timepoint