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# Accelerated aging in bipolar disorders : an exploratory study of six epigenetic clocks

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## Abstract

Bipolar disorder (BD) is a chronic and severe psychiatric disorder associated with significant medical morbidity and reduced life expectancy. In this study, we assessed accelerated epigenetic aging in individuals with BD using various DNAm (methylation)-based markers. For this purpose, we used five epigenetic clocks (Horvath, Hannum, EN, PhenoAge, and GrimAge clocks) and a DNA methylation-based telomere length clock (DNAmTL). We also estimated blood cell counts based on DNA methylation levels for adjustment. DNAm profiles were obtained using Infinium MethylationEPIC Arrays from whole-blood samples of 184 individuals with BD. Significant correlations between chronological age and each epigenetic age estimated using the six different clocks were observed (all p-values <0.001). Following adjustment for blood cell counts, 47 to 53% of the individuals with BD in our sample present with an epigenetic age acceleration (AgeAccel) whatever the epigenetic clock used. We also found that the six epigenetic AgeAccel were significantly associated with the BMI. Smoking status was significantly associated with GrimAge and DNAmTL AgeAccel. Childhood maltreatment was associated with GrimAge AgeAccel. Overall, this study identified an accelerated epigenetic aging in BD and some potential determinants.

## 1. Introduction (Background)

Bipolar disorder (BD) is a chronic and severe psychiatric disorder, characterized by the alternance of episodes of (hypo)-mania and major depression (Zhou et al., 2021). BD affects more than 1% of the general population (Grande et al., 2016) and is ranked at the 6<sup>th</sup> place of the leading causes of disability in the world (Colombo et al., 2012).

A ten to fifteen years decrease in life expectancy has been repeatedly observed in individuals with BD as compared to the general population (Chang et al., 2011; Crump et al., 2013; Weyer et al., 2020). This is due not only to higher rates of death by suicide (Crump et al., 2013), but also to increased rates of cardiovascular diseases, diabetes, or chronic obstructive pulmonary diseases as examples (Crump et al., 2013; Mutz et al., 2022b; Zareifopoulos et al., 2018). As a whole, individuals with BD present with higher rates of age-related medical conditions and higher levels of frailty (Mutz et al., 2022b, 2022a; Rizzo et al., 2014; Roshanaei-Moghaddam and Katon, 2009). Therefore, an accelerated aging has been suggested in individuals with BD (Rizzo et al., 2014), which has been so far mainly described by studies investigating telomere shortening (Fries et al., 2017; Powell et al., 2018; Spano et al., 2022; Squassina et al., 2017) or decreased mitochondrial DNA copy number (Kampmann, 1987; Spano et al., 2022; Yamaki et al., 2018). The association between BD and telomere shortening has been confirmed in a meta-analysis including 10 studies and 579 patients and 551 controls (Huang et al., 2018).

Another method to estimate accelerated cellular aging is based on patterns of changes in DNA methylation levels of specific CpG sites in the genome (which characterized “epigenetic clocks”). Indeed, DNA methylation is modified with age (Fransquet et al., 2019) and these modulations of DNA methylation patterns have been repeatedly validated as biomarkers of aging, in several tissues, including blood samples. Several epigenetic clocks definitions have been proposed to estimate epigenetic ages even in a disease context (Duan et al., 2022). Each epigenetic clock is based on methylation levels of a specific set of CpGs with very little between-sets overlap (Bell et al., 2019). The most commonly used epigenetic clocks were first described respectively by Hannum and Horvath (Hannum et al., 2013; Horvath, 2013). The EN (Elastic Net) clock was developed to increase the precision of the estimated age acceleration (Zhang et al., 2019). Two other epigenetic clocks, GrimAge and PhenoAge that were more

based on mortality and morbidity (Levine et al., 2018; Lu et al., 2019a), are also among the most commonly studied. Finally, a DNA methylation-based telomere length (DNAmTL), based on 140 CpGs, has been suggested to be linked to telomere length (Lu et al., 2019b).

Epigenetic age is still poorly studied in BD. Nevertheless, a few studies investigated this issue and its association with BD and/or its clinical presentation. Recently, *Jeremian* and colleagues found that epigenetic ages of individuals with BD were significantly higher than chronological age for four different epigenetic clocks (Horvath, Horvath Skin & Blood, Hannum and PhenoAge) but not for DNAmTL (Jeremian et al., 2022). *Fries* and colleagues published two studies using epigenetic clocks based on the Horvath clock in individuals with BD. In one study, they observed a significant epigenetic age acceleration in individuals with BD over 33 years old as compared to healthy controls. In this group of older individuals, epigenetic age was correlated with another biomarker of cellular aging which is the copy number of mitochondrial DNA (Fries et al., 2017). In hippocampal tissues, the same research group reported that another biomarker of aging (telomere length) correlated with the epigenetic age acceleration (AgeAccel) estimated using the Horvath epigenetic clock. A significant accelerated aging as compared to controls in the "older" group of individuals with BD, was also observed (Fries et al., 2020). Other studies focused on clinical variables such as current (or past) use of mood stabilizers or cognitive variables in individuals with BD (Lima et al., 2022; Okazaki et al., 2020). Mood stabilizers when used in combination in individuals with BD have been suggested to be associated with a significant decrease of the Horvath accelerated aging as compared to monotherapy with mood stabilizers or absence of currently prescribed mood stabilizers. This effect was not observed using the Hannum, GrimAge and DNAmTL epigenetic clocks (Okazaki et al., 2020). Using GrimAge, *Lima* and colleagues showed that individuals with BD present a higher AgeAccel than healthy controls. A higher acceleration was observed when cognitive functions such as short-term affective memory or inhibition were altered (lower short-term affective memory, higher inhibition) (Lima et al., 2022).

In the present study, we used six epigenetic clocks: five that are predictive of accelerated aging, mortality and morbidity (Hannum, Horvath, EN, GrimAge, PhenoAge) and one linked to telomere length (DNAmTL) to estimate the epigenetic age of 184 individuals with BD using DNA methylation data obtained from whole blood samples. The associations with basic clinical variables were then investigated.

## 2. Material and methods

### 2.1 Sample description and clinical assessment

This study was approved by the Comité de Protection des Personnes - La Pitié-Salpêtrière hospital – Paris - France (ClinicalTrials.gov Identifier: NCT02572674). All participants provided written informed consent prior to inclusion.

The sample consisted of 184 euthymic individuals with a diagnosis of BD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) criteria. Participants were recruited in eight university-affiliated psychiatric departments in France. Inclusion criteria for this study were as follow: Caucasian origin; age between 18 years and 55 years; and scores below 10 at the Montgomery–Asberg depression rating scale (Montgomery and Asberg, 1979) and 12 at the Young Mania Rating Scale (Bech et al., 1978) at inclusion.

The SCID (Structured Clinical Interview for DSM Disorders) was used to confirm the diagnosis of BD. Childhood traumatic events exposure was assessed with the French validated version of the Childhood Trauma Questionnaire (Bernstein and Fink, 1998; Paquette et al., 2004). For all participants, the database contained basic information such as age, sex, Body Mass Index (BMI), smoking status. Current alcohol misuse and past or current substance misuse were exclusion criteria. Information about the number of major mood episodes, age at onset of BD, current prescribed medications (antidepressants, atypical antipsychotics, lithium and anticonvulsants) were also recorded into the database.

### 2.2 DNA extraction and methylation measurement

A blood sample was collected at inclusion and whole blood DNA was extracted using the automated Maxwell 16 DNA Purification Instrument and the dedicated Maxwell® RSC Blood DNA Kit (Promega). Whole blood DNA samples were treated with sodium bisulfite using the EZ DNA methylation kit (Zymo Research, CA, USA) following the manufacturer's standard protocol. Methylation analysis was performed using Illumina Infinium MethylationEPIC Arrays (Illumina, Inc. San Diego, USA) at Diagenode facilities (Diagenode, Belgium). The Illumina GenomeStudio software was used to extract the raw signal intensities of each probe (raw beta

values) from the array. After quality control and normalization, the beta values were used for further analyses.

As previously described, real-time quantitative polymerase chain reaction (PCR) was used to measure telomere length (Spano et al., 2022) (Supplementary data 1).

## 2.4 Blood cell-type composition analysis

The analysis of the blood cell-type composition was performed using the Houseman method (Houseman et al., 2012). The overall proportions of the different cell types were determined using the minfi package and the estimateCellCounts function (Aryee et al., 2014), with the DNA methylation data as input. The proportions of CD4+ T cells, CD8+ T cells, B cells, Natural Killer cells, Monocytes and Granulocytes were then determined.

## 2.5 Epigenetic clocks and age acceleration calculations

Six epigenetic clocks have been selected in order to calculate epigenetic ages: Hannum, Horvath, EN, GrimAge, PhenoAge and DNAmTL. The Hannum, Horvath and EN epigenetic age were calculated using the MethClock R package (Pelegí-Sisó et al., 2021). The PhenoAge, GrimAge and DNAmTL epigenetic clocks were calculated using the PC Clocks R package (Higgins-Chen et al., 2022).

As previously proposed, epigenetic AgeAccel were calculated, for the six epigenetic clocks (Horvath, Hannum, EN, GrimAge and PhenoAge), using the residuals from regressing epigenetic age on the chronological one (Cerveira de Baumont et al., 2021; Yan et al., 2020).



## 2.7 Statistical analyses

All the statistical analyses were performed using R version 4.2.1 ([www.r-project.org](http://www.r-project.org)). Categorical variables were described as number and percentages. Continuous variables were described as median and IQR or mean and SD as appropriate. We mainly used non-parametric tests. The correlation statistics and charts were done using the PerformanceAnalytics R package (Peterson, 2022) and the corrr package (Kuhn et al., 2022). The network plots were realized using this corrr package. Spearman correlations were used, and p-values <0.05 were considered statistically significant.

The Wilcoxon effect size  $r$  (ranging between 0 and 1) was used to calculate the effect size in order to create Forest plots to visualize the results of associations with socio-demographic and clinical variables. The BMI under 25 ("normal BMI") were noted 0 and 1 over 25. For the other variables the values were divided by the median in our sample: "0" is noted for the sample under the median and "1" for the sample upper the median. All correlations presented in this study were adjusted for blood cell composition.

### 3. Results

Characteristics of the 184 individuals with BD (110 women and 74 men) are shown in Table 1. The mean age of this cohort is 38.82 years old (sd: 9.89). Most individuals (n=126, 68.5%) had a diagnosis of BD type 1. The mean number of major depressive episodes is 4.42 (sd=3.730, from 0 to 20) and the mean number of (hypo)manic episodes is 1.62 (sd=2.251, from 0 to 17). The mean BMI is 25.97 (sd: 4.66), 42.4% of the subjects are current smokers. The mean CTQ total score in this sample was 39.05 (sd: 12.78). Participants are currently treated with anticonvulsants (40.2%), lithium (31.5%), atypical antipsychotics (27.7%) and antidepressants (22.8%).

<b>Characteristics</b>	<b>Mean (or number) of each variable</b>
<b>Age</b>	38.82 (sd: 9.89)
<b>Sex</b>	110 Women (59.8%) & 74 Men
<b>Bipolar disorder</b>	126 type I (68.5%) & 55 type II - [3 missing]
<b>Major depressive episodes</b>	4.42 (sd: 3.730)
<b>(Hypo)manic episodes</b>	1.62 (sd: 2.251)
<b>Smoking status</b>	75 current (42.4%) ; 30 former ; 78 never – [1 missing]
<b>BMI (Body Mass Index)</b>	25.97 (sd: 4.66)
<b>CTQ (Childhood Trauma Questionnaire)</b>	39.05 (sd: 12.78)
<b>Antidepressants</b>	42 yes (22.8%) ; 115 no ; 27 missing
<b>Atypical antipsychotics</b>	51 yes (27.7%) ; 103 no ; 30 missing
<b>Lithium</b>	58 yes (31.5%) ; 65 no ; 61 missing
<b>Anticonvulsants</b>	74 yes (40.2%) ; 50 no ; 60 missing

Table 1: Characteristics of the individuals with BD included in this study. The means of the different variables are mentioned, as well as the standard deviation (noted "sd"). Some variables were not available for some patients ("missing" mention).

In order to analyze the relationships between the six epigenetic clocks used: Horvath, Hannum, EN, GrimAge, PhenoAge and DNAmTL, we perform a network analysis based on the calculated epigenetic ages in this sample that is described in Figure 1. Horvath, Hannum and EN epigenetic ages are closely connected while the GrimAge epigenetic age, a predictor of mortality, is more distant. The other epigenetic predictor of mortality, PhenoAge, is more connected to the Horvath, Hannum and EN epigenetic ages than the GrimAge age in our sample. As expected, the DNAmTL age, which reflects telomere shortening, is the farthest in this network and the links between DNAmTL age and the other epigenetic clocks are negative, in contrast to the links between the five other epigenetic clocks that are positive.

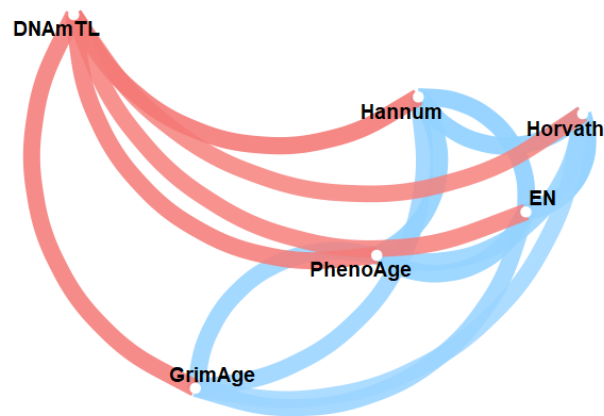


Figure 1: Network plot obtained for the six different epigenetic ages analyzed in our sample.

As shown in Figure 2, the epigenetic ages calculated with each of the five epigenetic clocks used are positively correlated with the chronological age of the patients, and the epigenetic ages are correlated with each other ( $p < 0.05$ ). Only the DNAmTL clock is negatively correlated with the other clocks. After adjustment for blood cellular composition, the correlations between epigenetic and chronological ages remain significant with rho values ranging from 0.85 (PhenoAge epigenetic clock) to 0.92 (EN epigenetic clock). As expected, the DNAmTL epigenetic clock shows a significant negative correlation with chronological age ( $r = -0.76$ ,  $p < 0.001$ ) in our sample (Figure 2). The correlations between epigenetic clocks are all significant and range between 0.84 (GrimAge and Horvath) and 0.94 (EN and Horvath). In the case of the DNAmTL epigenetic age, the correlations are significant with the other clocks, with negative correlations ranging between -0.83 (with EN and Horvath) and -0.88 (with Hannum).

However, this epigenetic age is not correlated with the telomere length as measured by qPCR in the cohort ( $r=0.142$ ,  $p=0.068$ ).

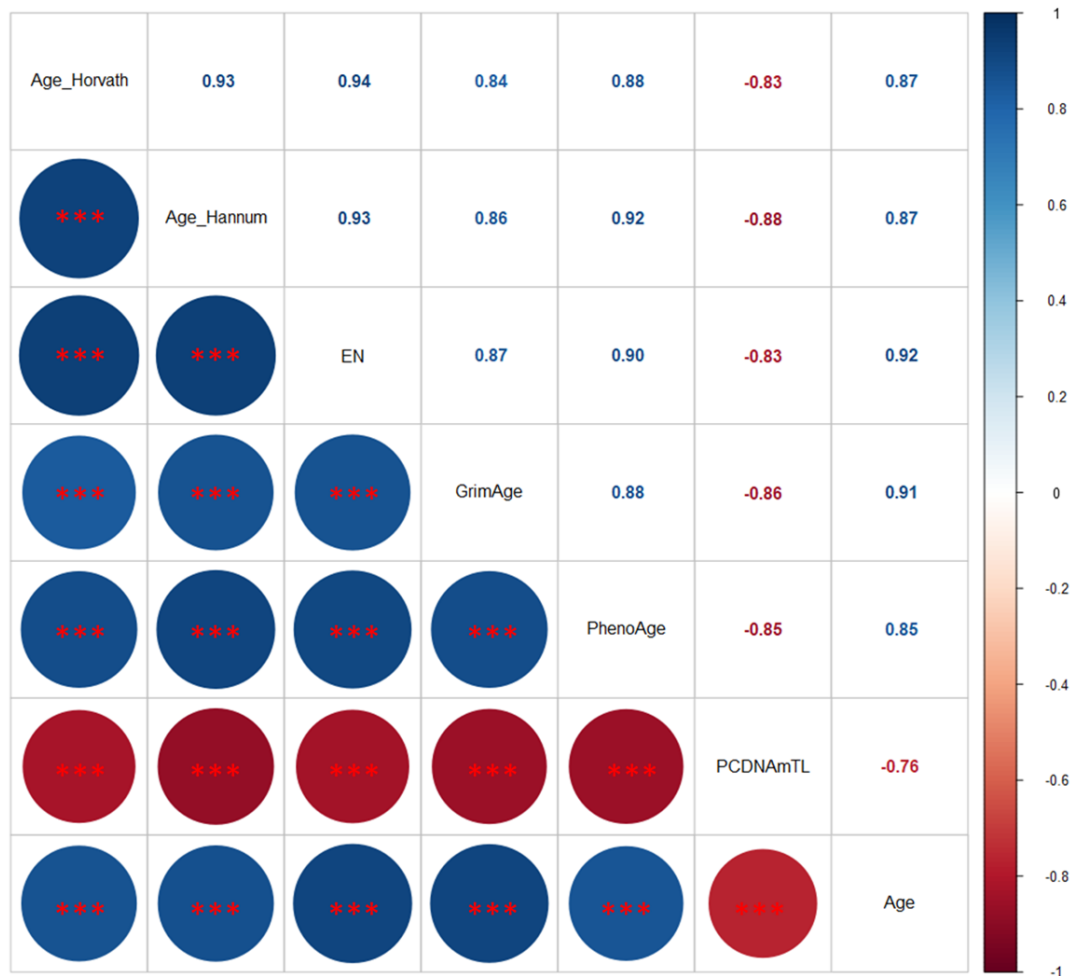


Figure 2: Significant correlations ( $p < 0.05$ ) between epigenetic clocks and chronological age, and between epigenetic clocks each other.

The AgeAccel values (adjusted for cellular composition), estimated using residuals, are presented as violin plots in Figure 3. The percentages of individuals with positive accelerated aging (suggestive of premature aging) according to the six different definitions are as follows: 49.91% of the sample show a positive AgeAccel in the Horvath clock, 50% for the Hannum clock, 53.80% for the EN clock, 47.28% for the GrimAge one, 51.09% for the PhenoAge clock and 49.46% for the DNAmTL clock.

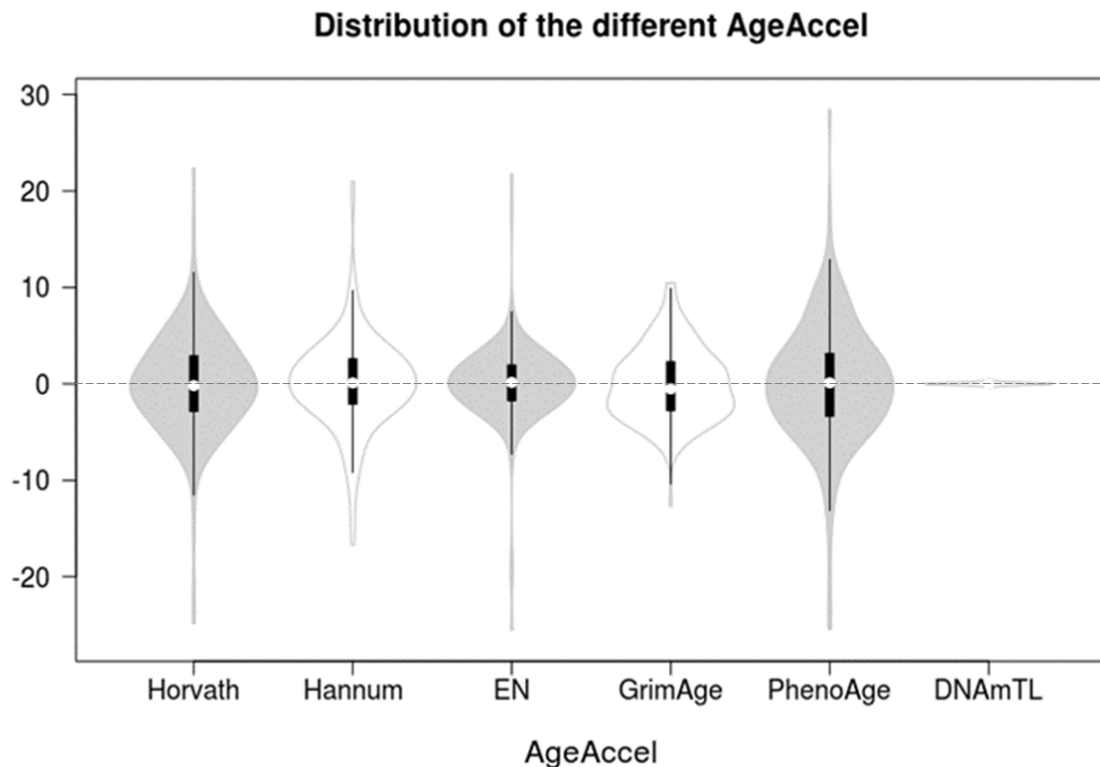


Figure 3: Distribution of the Horvath, Hannum, EN, GrimAge, PhenoAge and DNAmTL AgeAccel (after adjustment for cellular composition). The dotted grey line represents a value of zero corresponding to the absence of accelerated aging

In order to visualize the associations between the clinical variables and the different AgeAccel (adjusted for the cellular composition), forest plots are presented in Figure 4.

A higher BMI is associated with all the six AgeAccel evaluated. Male sex is associated only with the Grim AgeAccel. The CTQ total score is associated only with GrimAge AgeAccel. Smoking status is significantly associated with both DNAmTL AgeAccel and GrimAge AgeAccel.

None of the other available clinical characteristics (age of onset, duration of BD, number of major episodes (depressive or manic), density of episodes (number of major episodes divided by the duration of BD)) are significantly associated with the different AgeAccel (Figure S1). Similarly, the uses of current medications (antipsychotics, lithium, anticonvulsants and antidepressants) are not associated with the different epigenetic AgeAccel. The effect of the number of treatments (mono- vs poly-therapy) on the epigenetic AgeAccel are not significant either (Figure S1).

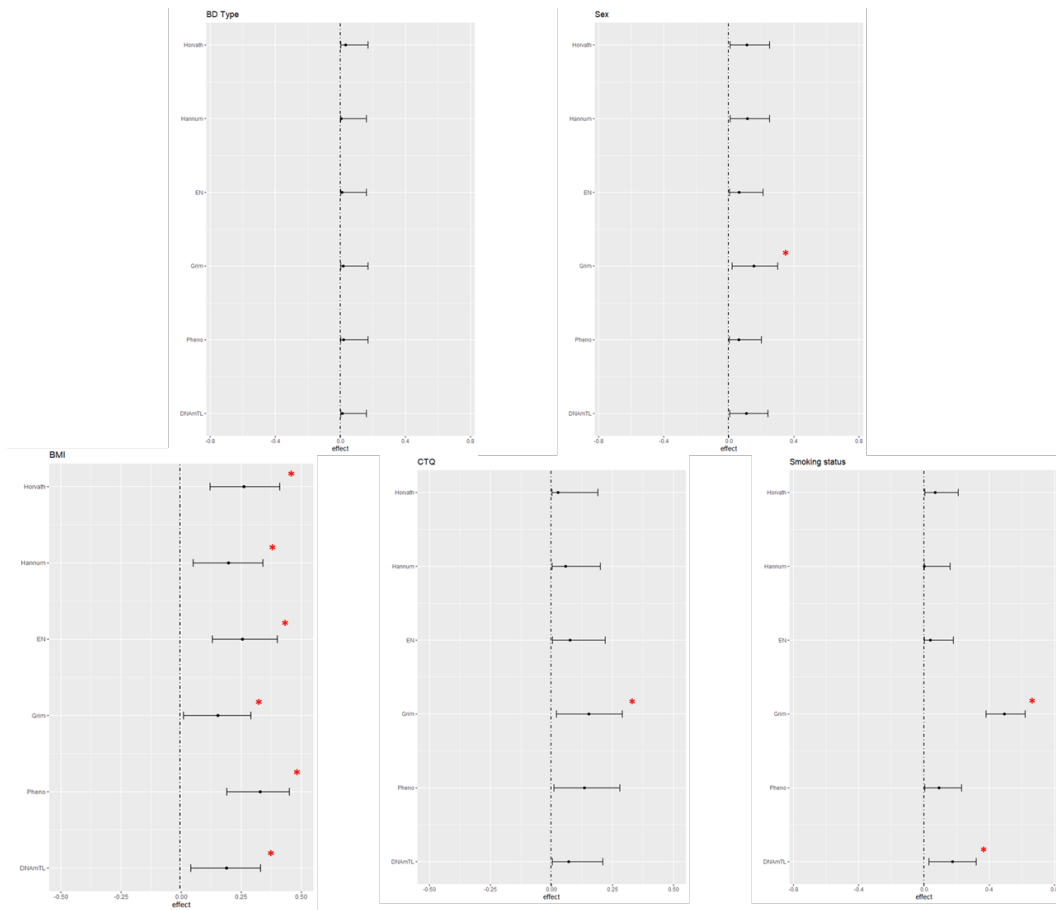


Figure 7: Forest plot of the different effect sizes of clinical variables on the six epigenetic AgeAccel. The significant correlations are mentioned by "\*" (p-value<0.05).

## 4. Discussion

This study shows highly significant correlations between chronological age and each epigenetic age estimated using six different clocks (Horvath, Hannum, EN, PhenoAge, GrimAge and DNAmTL) in a sample of individuals with BD. As expected, DNAmTL epigenetic age was significantly negatively correlated with chronological age and with the other epigenetic ages. Forty-seven to fifty-three percent of the individuals with BD in our sample may be considered as having an epigenetic age acceleration depending on the epigenetic clock used. We also found that the six epigenetic AgeAccel were significantly associated with the BMI. In addition, GrimAge AgeAccel was associated with smoking status, sex and childhood maltreatment, while DNAmTL AgeAccel was associated with smoking status only.

The strong correlations obtained between the six estimated epigenetic ages and the chronological age showed the relevance of the epigenetic clocks to study accelerated aging in our sample. This is consistent with previously reported epigenetic age estimations in individuals with BD (Okazaki et al., 2020). However, the six epigenetic clocks used here (Hannum, Horvath, EN, GrimAge, PhenoAge and DNAmTL) are based on different CpGs and are likely to reflect distinct aging processes (Hamlat et al., 2021). This is illustrated with the network analysis, with GrimAge and PhenoAge being more distant from the others (Horvath, Hannum and EN). As previously described, this may result in discrepancies in results between studies because of the chosen CpG used in the different clocks (Wolf et al., 2018). DNAmTL is described as a DNA methylation-based TL marker (Lu et al., 2019b), our results showing a narrow distribution of this variable is consistent with previously published data (Seki et al., 2023; Shi et al., 2022). The residuals of DNAmTL present a similar distribution, as previously reported in several pathologies (Hernández Cordero et al., 2021; Shinko et al., 2022). DNAmTL, which is described as a DNA methylation-based TL marker (Lu et al., 2019), was not correlated with the measured TL in our sample. This lack of correlation is also consistent with previous findings. For instance, Lu and colleagues expressed that the epigenetic clock (DNAmTL) is more strongly linked with age than with the leukocyte telomere length measurements (Lu et al., 2019).

We observed several associations between age accelerations and the clinical variables investigated in this sample. All epigenetic AgeAccel used in this study showed significant associations with BMI. This result is consistent with two previous studies, showing an association of BMI with epigenetic aging (Oblak et al., 2021; Quach et al., 2017). In addition, a

recent meta-analysis shows that BMI is positively associated with a higher epigenetic age in half of the 10 studies analyzed (Ryan et al., 2020). Among studies showing no associations, two had small samples and one shows only a weak correlation between epigenetic age and chronological age (Simpkin et al., 2017). Moreover, a study based on twins highlights a strong association between BMI and epigenetic age, comparing epigenetic age acceleration using GrimAge between the heavier and the lighter twins (Lundgren et al., 2022). Smoking status was also found positively associated only with GrimAge AgeAccel and DNAmTL AgeAccel in our study. This may be due to the fact that the GrimAge clock was built by directly incorporating smoking-related changes with an estimated “pack-years” smoking (Lu et al., 2019a). Our result is therefore consistent with previous studies showing, for current smokers reporting > 100 cigarettes in their lifetime, an age acceleration for GrimAge (6.36 years), in comparison with individuals who never smoked (Cardenas et al., 2022). The result we obtained with DNAmTL AgeAccel is consistent with previous results observed in a meta-analysis, showing a strong association between DNAmTL AgeAccel and smoking (Lu et al., 2019b).

The Forest plot visualization further showed a significant association between the CTQ total score and the GrimAge AgeAccel only. This is consistent with previous results in 1445 individuals from the Canadian Longitudinal Study on Aging, where GrimAge Accel was found to be associated with the adverse childhood exposure score and also with the presence of emotional abuse (Joshi et al., 2023). In addition, childhood abuse exposure (but not neglect) was also found associated with faster epigenetic aging with GrimAge in a sample of 183 premenopausal mothers (Hamlat et al., 2021). A meta-analysis showed that childhood trauma exposure increases inflammation in adulthood (Baumeister et al., 2016). Moreover, this increase of inflammation has been suggested to contribute to premature aging (Merz and Turner, 2021; Renna et al., 2021). As previously mentioned, the GrimAge and PhenoAge clocks, based on mortality and morbidity, might be more sensitive to this aging process as compared to the other clocks based on biological age and/or telomere length (Levine et al., 2018). In line with this hypothesis, Rampersaud and colleagues showed a significant association between PhenoAge AgeAccel but not with GrimAge, Horvath nor Hannum AgeAcceleration in 81 individuals with major depressive disorder and childhood maltreatment (Rampersaud et al., 2022).



As suggested by a meta-analysis, epigenetic clocks could become a tool to estimate mortality risk in the general population but also for individuals with BD (Fransquet et al., 2019). The identification of clinical variables associated with an increased AgeAccel would allow a better stratification of the patients most at risk. These at-risk patients could therefore be better monitored, including through interventions that would help slowing epigenetic age acceleration, including - based on our results - interventions for promoting healthy diet and smoking cessation for example.

Among the limitations of this study, we acknowledge the cross-sectional design of the present study that prevents any conclusion about causality and a moderate sample size. However, this is, so far, the largest BD sample combining the analyses of several epigenetic clocks. In addition, we investigate for the first time in individuals with BD the association between several clinical variables such as childhood adversity, smoking and BMI and an accelerated aging. Another limitation is that we could not obtain information on several confounders such as physical activity, sleep or diet. This information would help to better characterize epigenetic aging in future studies of accelerated aging in BD.

## Conclusion

In conclusion, we investigated six epigenetic clocks (Horvath, Hannum, EN, PhenoAge, GrimAge and DNAmTL) and their associations with basic clinical variables in individuals with BD. All epigenetic clocks were correlated with chronological age in individuals with BD. We provide evidence of an epigenetic age acceleration in about half of the participants, depending on the epigenetic age definitions. Moreover, this is the first study that identifies some potential determinants of accelerated epigenetic aging in BD, such as childhood maltreatment, higher BMI or smoking status. Large-scale and longitudinal studies incorporating well-documented lifestyle parameters are needed to better identify the determinants of accelerated aging in BD. These studies are anticipated to improve the management of patients who are likely to be at greater risk of accelerated aging and age-related pathologies in a context of personalized medicine in BD.





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## Author contributions

BE and CM-C designed the study. CB and LS performed the experiments. CB performed all data analysis and interpretation with inputs from BE and CM-C. CB drafted and revised the manuscript. BE and CM-C reviewed and edited the manuscript. BE, RB, ML, SG, RS, MP, PC and CP contributed to the recruitment of participants. FB obtained the funding for the clinical recruitment and supervised the project. BE and CM-C obtained the funding for the methylation data generation. All authors commented on the manuscript and approved the final version of the manuscript.

## Conflict of interest

None to be declared in links with this study.

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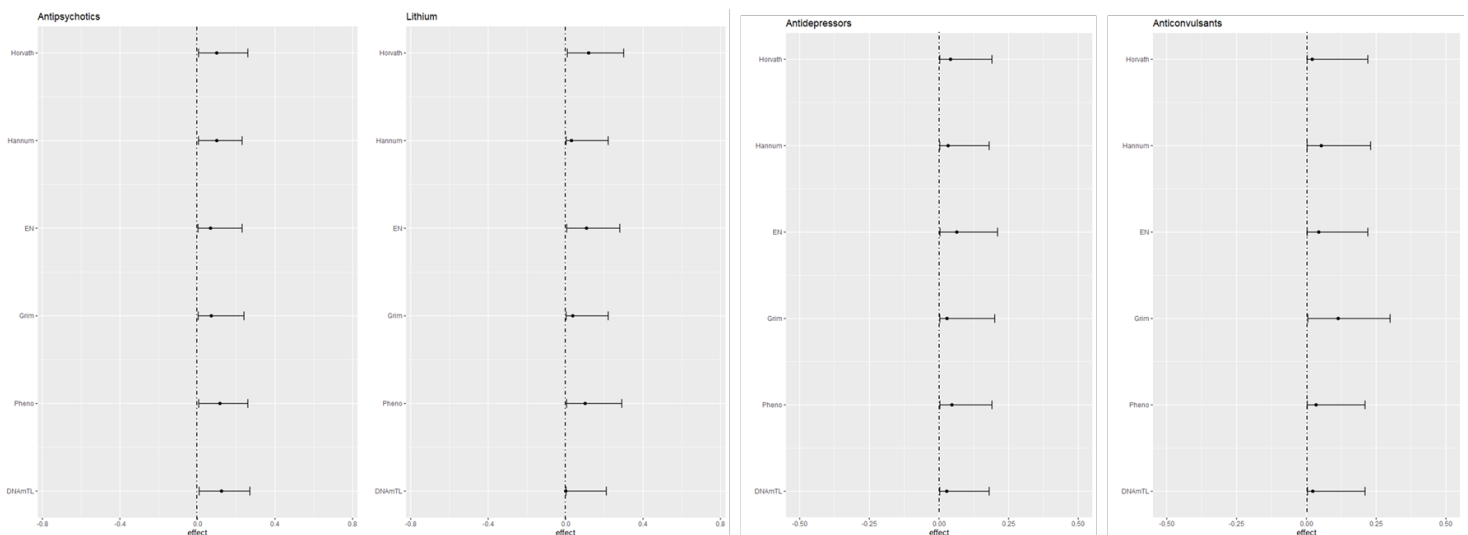
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**SUPPLEMENTARY TABLE 1**

<b>Epigenetic clocks</b>	<b>Number of CpG</b>	<b>Number of samples</b>	<b>Tissues</b>
Hannum	71	656 (19-101 years old)	Blood
Horvath	353	8000	51 tissues
EN	514	13661 (2-104 years old)	Blood/Saliva
PhenoAge	513	456 (21-100 years old)	Blood
GrimAge	1030	2356	Blood
DNAmTL	140	2256	Blood

Supplementary Table 1: Characteristics of the six different epigenetic clocks analyzed in this study. The number of CpG and samples used in order to create each one are mentioned, as well the tissue. The Hannum clock is one of the first epigenetic clocks created, from 71 CpG regions of 656 samples. The Horvath and EN clocks used higher numbers of CpG (respectively 353 and 514 CpG) and samples (respectively 8000 and 13661 people). The PhenoAge and GrimAge are two epigenetic clocks based on mortality and morbidity. The DNAmTL is an estimation of the telomere erosion, based on 140 CpG and 2256 persons.

**Supplementary figure 1 :**



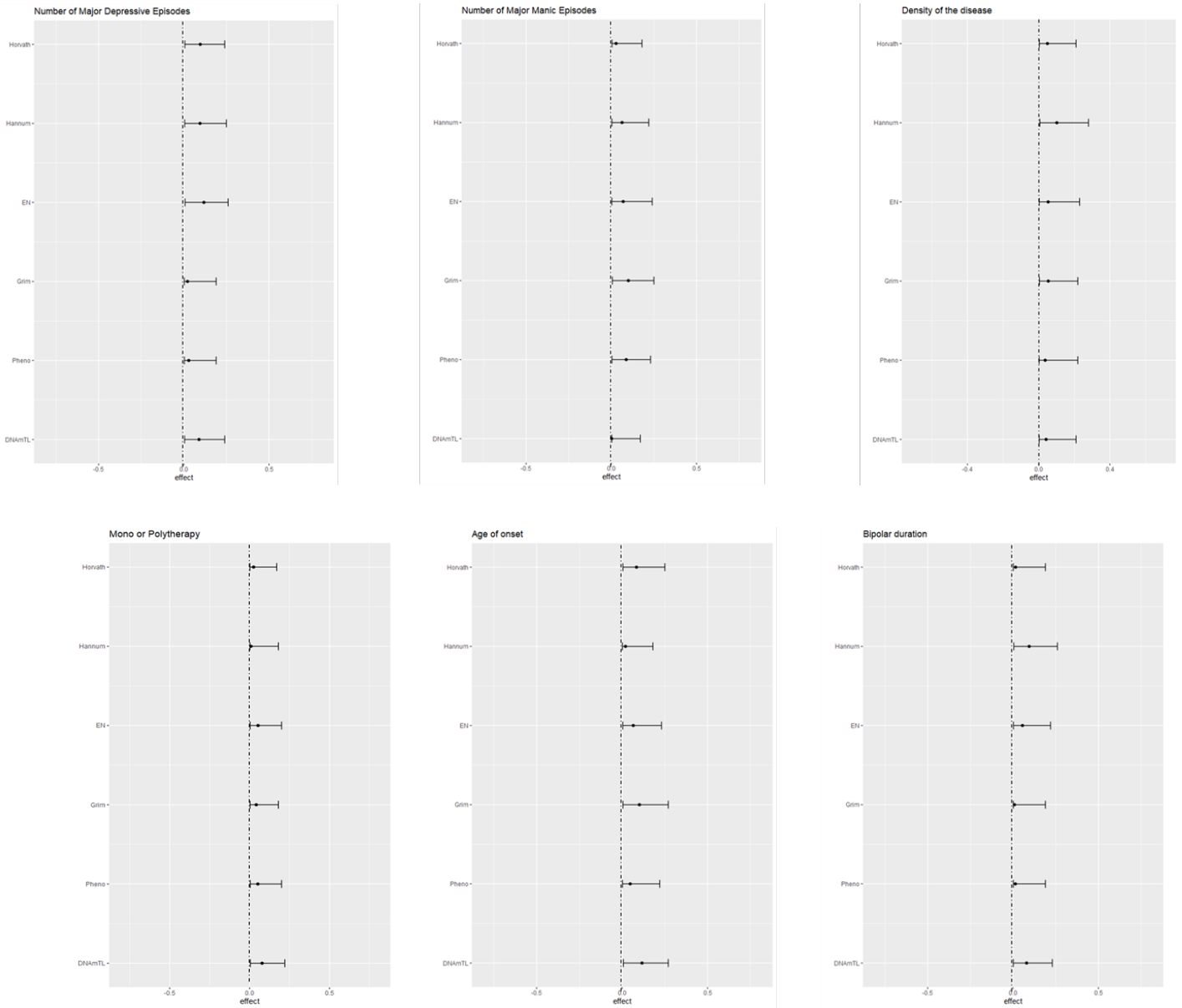


Figure S1: Forest plot of the different effect sizes of clinical variables on the six epigenetic AgeAccel.

### Supplementary data 1: Telomere length measure

Briefly, Beta-hemoglobin gene was used as single-copy standard for a relative quantification of TL and all samples were assessed in triplicate. The final equation for T/S ratio was the normalized expression (NE) between RQ of telomere and RQ of our reference gene beta-hemoglobin ( $NE = RQ_{telomere}/RQ_{beta-hemoglobin}$ ) (Spano et al., 2022).