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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 DNA methylation (DNAm)-based markers. For this purpose, we used five epigenetic clocks (Horvath, Hannum, EN, PhenoAge, and GrimAge) and a DNAm-based telomere length clock (DNAmTL). DNAm profiles were obtained using Infinium MethylationEPIC Arrays from whole-blood samples of 184 individuals with BD. We also estimated blood cell counts based on DNAm levels for adjustment. Significant correlations between chronological age and each epigenetic age estimated using the six different clocks were observed. Following adjustment for blood cell counts, we found that the six epigenetic AgeAccels (age accelerations) were significantly associated with the body mass index. GrimAge AgeAccel was significantly associated with male sex, smoking status and childhood maltreatment. DNAmTL AgeAccel was significantly associated with smoking status. Overall, this study showed that distinct epigenetic clocks are sensitive to different aspects of aging process in BD. Further investigations with comprehensive epigenetic clock analyses and large samples are required to confirm our findings of potential determinants of an accelerated epigenetic aging in BD.

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## 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 6th 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; Weye 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., 2022a; 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). This phenomenon 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 (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 including 579 patients and 551 controls (Huang, 2018), while results remained inconsistent for mitochondrial DNA copy number in a recent meta-analysis including 284 patients and 201 control subjects (Yamaki et al., 2018).

Another method to estimate accelerated cellular aging is based on patterns of changes in DNA methylation (DNAm) levels of specific CpG sites in the genome (which characterize “epigenetic clocks”). Indeed, DNAm 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 mainly 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 associated with 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 the clinical presentation of the disorder. 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: 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). A few additional 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). This group also found, in two distinct samples, that patients with BD and with history of suicide attempt show a higher GrimAge acceleration than healthy controls or patients with BD without history of suicide attempt (Lima et al., 2023).

In the present study, we intend to replicate and to extend previous findings using epigenetic clocks in individuals with BD. We chose to use six epigenetic clocks: five that are predictive of accelerated aging, mortality and morbidity (Hannum, Horvath, EN, GrimAge, PhenoAge) and one associated with telomere length (DNAmTL) to estimate the epigenetic age of 184 individuals with BD using DNAm data obtained from whole blood samples. In addition, we investigated the associations between epigenetic age accelerations and basic socio-demographic and clinical variables (including age, sex, body mass index, tobacco use, childhood maltreatment, current use of psychotropic drugs and several indicators of BD course).

## 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 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 (Young 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 (CTQ) (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. Methylome 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. These beta values were used for further

analyses of epigenetic clocks, as recommended (Higgins-Chen et al., 2022; Pelegí-Sisó et al., 2021). Poor quality probes were excluded based on detection p-values < 0.01 using the minfiR package (Aryee et al., 2014).

Details of the previously described (Spano et al., 2022) real-time quantitative polymerase chain reaction (PCR) to measure telomere length are provided as supplementary material (Supplementary data 1).

### 2.3. 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.

### 2.4. Epigenetic clocks and age acceleration calculations

Six epigenetic clocks have been selected to calculate epigenetic ages: Hannum, Horvath, EN, GrimAge, PhenoAge and DNAmTL. The Hannum, Horvath and EN epigenetic age were calculated using the Methylation 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 five 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).

### 2.5. Statistical analyses

All the statistical analyses were performed using R version 4.2.1 (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 constructed using the corrr package, based on a multidimensional clustering in order to determine the distance between the variables: this package used the absolute values of the correlations as the proximity/distance metric. 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 to create Forest plots to visualize the results of associations between AgeAccel and socio-demographic and clinical variables. A BMI under 25 ("normal BMI") was coded 0 or 1 if over 25. For the other variables, the values were categorized using the median of our sample: "0" was coded for the individuals with values lower than the median and "1" for the individuals with values higher than 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%) have a diagnosis of BD type 1. The mean number of major depressive episodes is 4.42 (SD=3.73, from 0 to 20) and the mean number of (hypo)manic episodes is 1.62 (SD=2.25, 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 was 39.05 (SD: 12.78). Participants are currently treated with anticonvulsants (40.2%), lithium (31.5%), atypical antipsychotics (27.7%) and

**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 (indicated as [missing]).

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

antidepressants (22.8%).

As shown in Fig. 1, 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 ( $p < 0.001$ ). 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 (Fig. 2). The correlations between epigenetic clocks are all significant and range between 0.84 (between GrimAge and Horvath) and 0.94 (between 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, DNAmTL epigenetic age is not correlated with the telomere length as measured by qPCR in the cohort ( $r = 0.142$ ,  $p = 0.068$ ) (the method used for qPCR telomere length measurement is available as supplementary data).

In order to analyze the relationships between the six epigenetic clocks used: Horvath, Hannum, EN, GrimAge, PhenoAge and DNAmTL, we performed a network analysis based on the calculated epigenetic ages which is described in Fig. 2. Horvath, Hannum and EN epigenetic ages are closely inter-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 (red color), in contrast to the links between the five other epigenetic clocks that are positive (blue color).

The AgeAccel values (adjusted for cellular composition), estimated using residuals, are presented as violin plots in Fig. 3. The percentages of individuals with positive accelerated 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.

In order to visualize the associations between the clinical variables and the different AgeAccel (adjusted for the cellular composition), forest plots are presented in Fig. 4. A higher BMI is associated with all the six AgeAccel evaluated. Male sex is associated only with the GrimAge AgeAccel. The CTQ total score is associated only with GrimAge AgeAccel, however without any specific associations with the two sub-domains of CTQ: "all neglects" and "all abuses" (data not shown). Smoking status is significantly associated with both DNAmTL AgeAccel



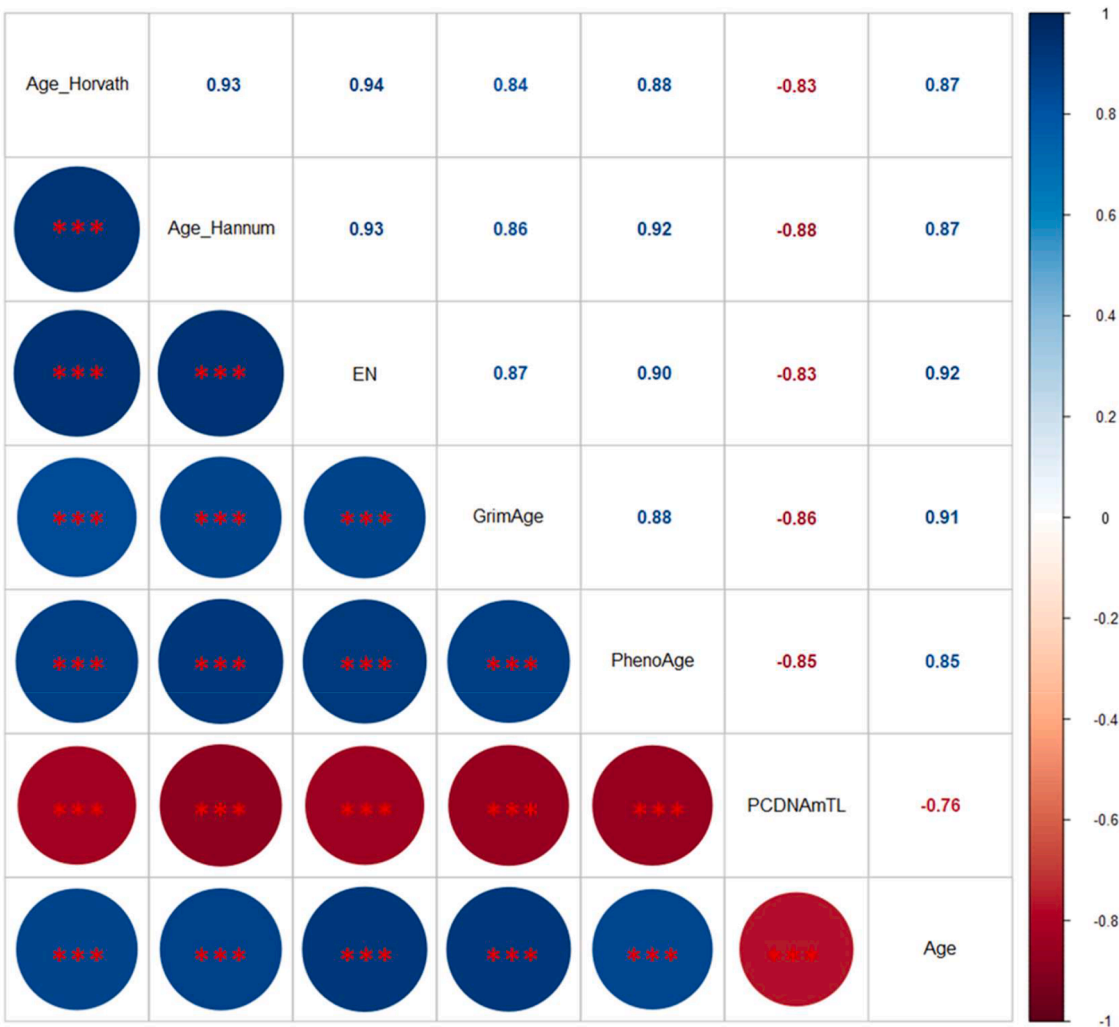


Fig. 1. Significant correlations (\*\*\*,  $p < 0.001$ ) between epigenetic clocks and chronological age, and between epigenetic clocks each other.

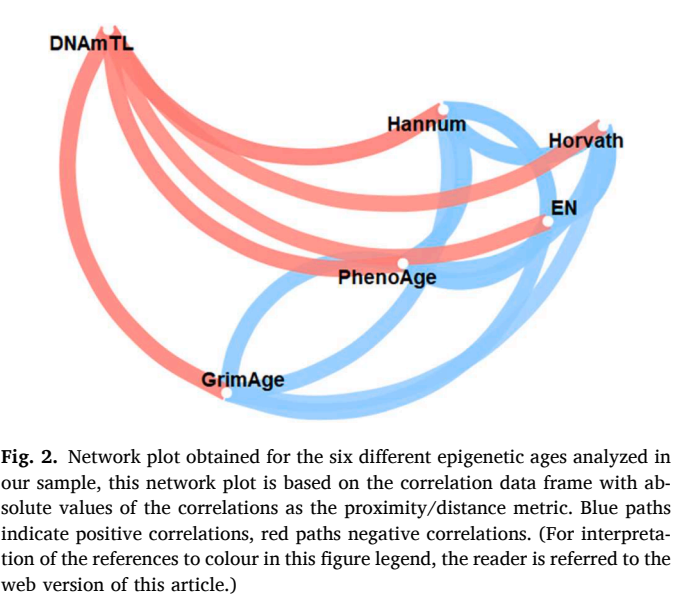


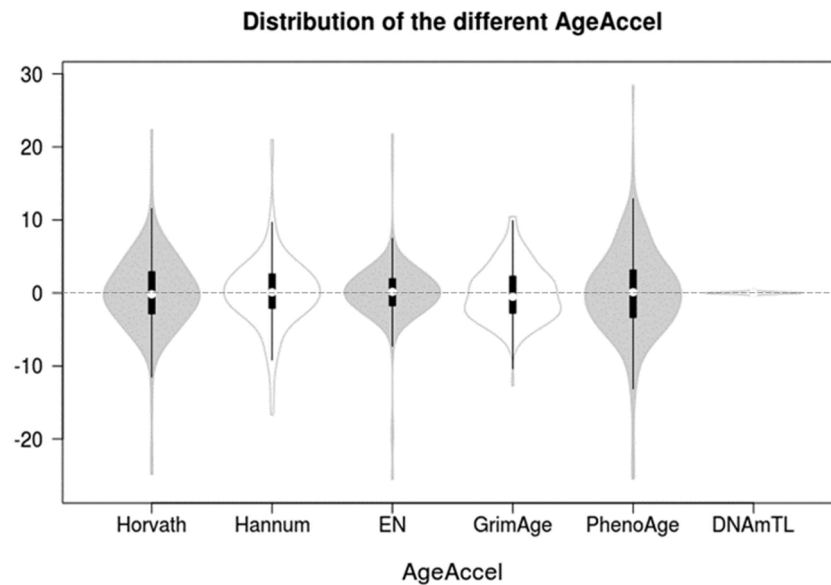
Fig. 2. Network plot obtained for the six different epigenetic ages analyzed in our sample, this network plot is based on the correlation data frame with absolute values of the correlations as the proximity/distance metric. Blue paths indicate positive correlations, red paths negative correlations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of episodes (number of major episodes divided by the duration of BD)) are significantly associated with the different AgeAccel (Supplementary Figure S1). Similarly, the uses of current medications (antipsychotics, lithium, anticonvulsants, and antidepressants) are not associated with the different epigenetic AgeAccel in our sample. The effect of the number of treatments (mono- vs. poly-therapy) on the epigenetic AgeAccel are not significant either (Figure S1).

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, male 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 suggested the relevance of these epigenetic clocks to study accelerated aging in our sample. This is consistent with previously reported epigenetic age estimations in



**Fig. 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.

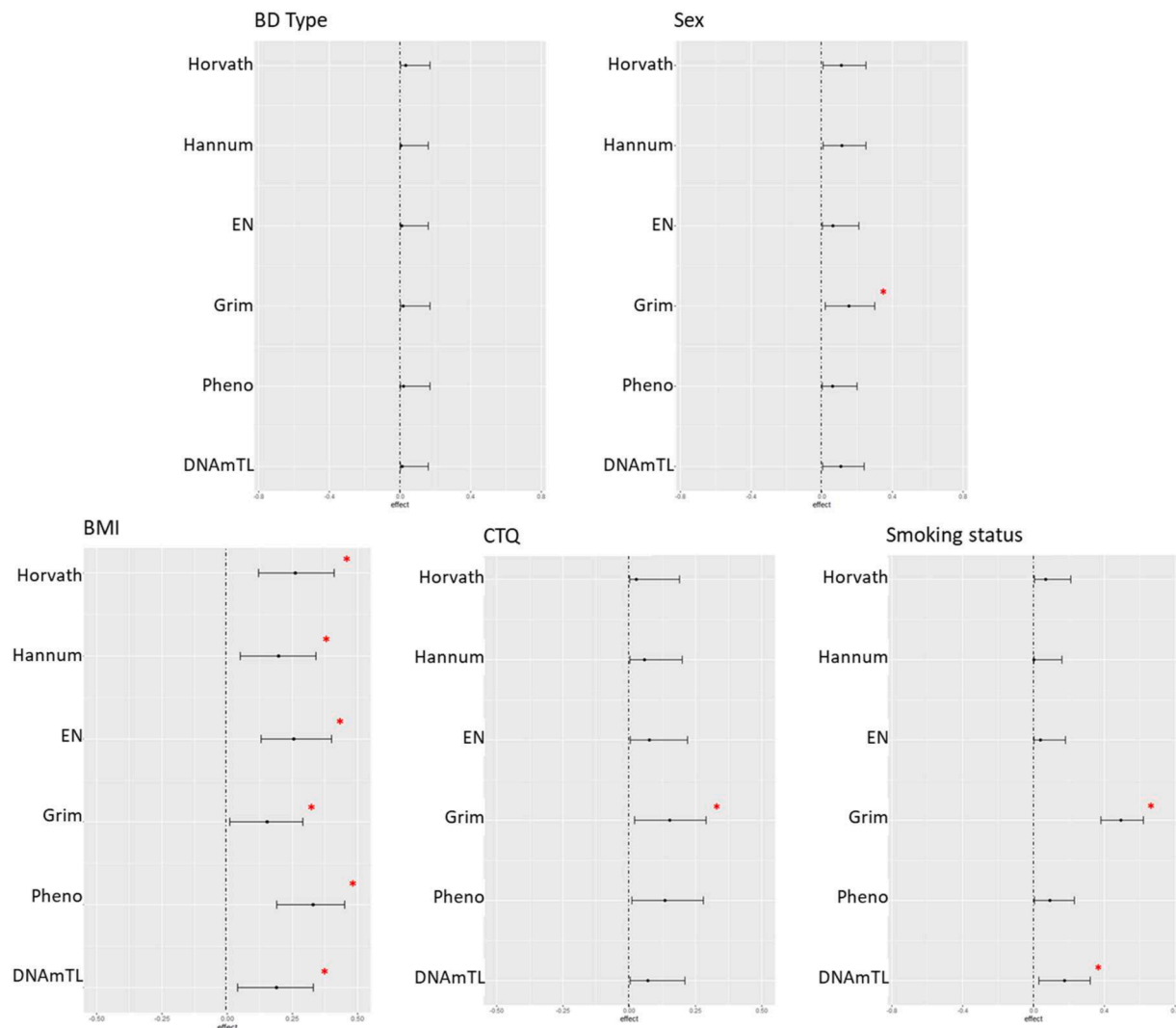
individuals with BD (Okazaki et al., 2020). However, the six epigenetic clocks used here (Hannum, Horvath, EN, GrimAge, PhenoAge and DNAmTL) are based on different CpGs and are likely to reflect distinct aging processes (Hamlat et al., 2021). This is illustrated with the network analysis, with GrimAge 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 those previously reported in several disorders or diseases (Hernández Cordero et al., 2021; Shinko et al., 2022). DNAmTL, which is described as a DNA methylation-based TL marker (Lu et al., 2019b), 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 concluded that the epigenetic clock (DNAmTL) is more strongly linked with age than with the leukocyte telomere length measurements (Lu et al., 2019b). Moreover, it has been suggested that methylation clocks and telomere length may quantify different mechanisms (namely genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, cellular senescence, and others) (Belsky et al., 2018; López-Otín et al., 2013). Another study found similar conclusions comparing telomere length and epigenetic clock (Marioni et al., 2016), and a recent study explains the differences seen between these two markers by the development of epigenetic age in a mathematically way with the aim to predict age, while the telomere length is a natural biological measurement of telomeres reflecting more directly a cellular process (Pearce et al., 2022).

We observed several associations between age accelerations and the clinical variables investigated in this sample. All epigenetic AgeAccel calculated in this study showed significant associations with BMI. This result is consistent with previous studies, in general population, showing an association between BMI and epigenetic aging (review in (Oblak et al., 2021)). 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 accelerated 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 and childhood maltreatment in 81 individuals with major depressive disorder (Rampersaud et al., 2022). Our results show a moderate association with CTQ ( $r = 0.153$ ). This result is nevertheless statistically significant, and is in line with other studies: in the study by Joshi and colleagues, the  $\beta$  of the multivariable linear regression model is  $\beta = 0.06$  and in the Hamlat study the  $b$  has a value of 0.09 (Hamlat et al., 2021; Joshi et al., 2023). No specific association was found for the two subdomains of the CTQ: “all neglects” and “all abuses”. However, some individuals had missing data for these subdomains



**Fig. 4.** Forest plot of the different effect sizes of clinical variables on the six epigenetic AgeAccel. The significant correlations are mentioned by a red asterisk (p-value < 0.05). (BD: Bipolar Disorder, BMI: Body Mass Index, CTQ: Childhood Trauma Questionnaire). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(since only the CTQ total score has been recorded in the database), leading to a possible lack of power. This issue would thus deserve further investigation in independent samples.

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. Of note, most of the associated factors (BMI, sex, smoking status and childhood adversities) are not specific to BD and we identified no specific factors to BD (such as course of the disorder or medications) that are associated to the epigenetic age accelerations. Therefore, at-risk patients could be better monitored through interventions that would help slowing epigenetic age acceleration, including - based on our results - interventions for promoting healthy diet and smoking cessation for example. In addition, pharmacological or microbiome-based interventions targeting epigenetic mechanisms have been recently proposed to promote prolonged healthy life span (Galow and Peleg, 2022).

Among the limitations, we acknowledge the cross-sectional design of the present study that prevents any conclusion about causality. In addition, the sample size, even though one of the largest studied to date with epigenetic age, remains moderate. Expanding sample size might improve the power of the analyses regarding associations between age

acceleration and clinical variables, especially for treatment variables and CTQ subdomains. The lack of a control subject group is another limitation that prevents any comparison between individuals with and without BD. However, this is, so far, the largest BD sample combining the analyses of several epigenetic clocks. In addition, we investigate in individuals with BD the association between several clinical variables such as childhood adversity, smoking status, BMI, current medications and clinical characteristics of BD with an accelerated aging. Another limitation is that information on the length of psychotropic treatment were not available in our database, nor information about several confounders such as physical activity, sleep or diet. These information would deserve further investigations in future studies of epigenetic accelerated aging in BD. Finally, replications in larger and independent are needed to confirm the main associations observed in our study.

## 5. 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. Moreover, this study explored clinical variables that have not been investigated before and leads to the identification of some potential determinants of

accelerated epigenetic aging in BD, such as childhood maltreatment, male sex, 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.

## CRediT authorship contribution statement

**Céline Bourdon:** Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Bruno Etain:** Conceptualization, Funding acquisition, Investigation, Supervision, Validation, Writing – review & editing. **Luana Spano:** Writing – review & editing. **Raoul Belzeaux:** Investigation, Writing – review & editing. **Marion Leboyer:** Investigation, Writing – review & editing. **Andrée Delahaye-Duriez:** Methodology, Writing – review & editing. **El Chérif Ibrahim:** Methodology, Writing – review & editing. **Pierre-Eric Lutz:** Methodology, Writing – review & editing. **Sébastien Gard:** Investigation, Writing – review & editing. **Raymund Schwan:** Investigation, Writing – review & editing. **Mircea Polosan:** Investigation, Writing – review & editing. **Philippe Courtet:** Investigation, Writing – review & editing. **Christine Passerieux:** Investigation, Writing – review & editing. **Frank Bellivier:** Funding acquisition, Project administration, Writing – review & editing. **Cynthia Marie-Claire:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing.

## Declaration of Competing Interest

None to be declared in links with this study.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2023.115373](https://doi.org/10.1016/j.psychres.2023.115373).

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