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Research paper

Telomere length and verbal learning in bipolar disorders

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ABSTRACT

Introduction: Recent studies indicate accelerated ageing processes, shorter telomere length and poorer cognitive functioning in patients with bipolar disorder. The neurobiology underlying cognitive function in bipolar disorder is yet to be established. We anticipated that accelerated ageing as indicated by shortened telomere length, would be associated with reduced cognitive performance in bipolar disorder, particularly for ageing sensitive functions such as memory and learning.

Methods: The study consisted of 647 participants (bipolar disorder [$n = 246$] and healthy controls [$n = 401$]). All participants underwent a standardized neuropsychological test battery, including working memory, executive functioning, processing speed, verbal learning, and verbal memory. Leucocyte telomere length was measured via blood and determined by quantitative real-time Polymerase Chain Reaction (qPCR) providing a telomere to single copy ratio (T/S ratio). The T/S ratio was used as an estimate of the mean telomere length of each participant. All analyses were adjusted for medication, Daily Defined Dose (DDD), chronological age, sex, and ethnicity.

Results: Patients had shorter telomere lengths than healthy controls (Cohen's $d = 0.11$, $p = 0.01$). Within patients', a positive association was observed for verbal learning and telomere length ($\beta = 0.14$, $p = 0.025$), along with a trend for verbal memory and telomere length ($\beta = 0.11$, $p = 0.07$). No other associations were observed for telomere length and cognitive functioning in the patient or the control group ($p > 0.1$).

Conclusion: Our study may suggest poorer brain health in bipolar disorder as indexed by shorter telomere length and reduced learning correlates. However, the role of telomere length on cognitive functioning in bipolar disorder seems limited.

1. Introduction

The lifespan of people with bipolar disorder (BD) is ten to fifteen years shorter than the general population (Hayes et al., 2015; Laursen, 2011), and patients with BD are at an increased risk of developing somatic diseases associated with advanced age, such as cardiovascular diseases and dementia (Launders et al., 2022; Hayes et al., 2015). Two recent reviews indicate accelerated ageing processes and poorer brain health in BD (Fries et al., 2020; Rizzo et al., 2014). Older age is associated with poorer cognitive performance, especially in verbal memory and learning tasks (Harada et al., 2013), and cognitive deficits are observed in BD (Bourne et al., 2013; Demmo et al., 2017; Simonsen

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et al., 2010). However, how cognitive abnormalities in BD may be related to accelerated ageing processes and poorer brain health is yet to be established.

Telomeres, repeating TTAGGG nucleotides, are located on the ends of all human chromosomes (Meyne et al., 1989), with shorter telomeres serving as an index of poorer brain health. Telomeres cannot be regrown (Hayflick and Moorhead, 1961). Once they are eroded and vital parts of DNA become exposed, cells will enter a state of senesce or undergo apoptosis (Blasco, 2007) that may cause deterioration of tissues, a process thought to be one of the explanations of ageing (Razgonova et al., 2020). Whilst telomeric degeneration is a universal process (Revy et al., 2023), epidemiological studies have noted differences in telomere length and its rate of reduction between the sexes (Wolkowitz et al., 2017), races (Brown et al., 2017), in Alzheimer's and Parkinson's disease (Yu et al., 2021), and in severe mental disorders, including BD (Savolainen et al., 2012, Darrow et al., 2016; Vakonaki et al., 2018). Only two studies have investigated the role of accelerated ageing indexed by telomere length for cognitive functioning in BD. The first study by Powell and colleagues consisting of 63 patients with BD demonstrated that poorer performance on a verbal long-term memory task was associated with having shorter telomere length (Powell et al., 2018). However, this study only investigated immediate and delayed memory without including a broader specter of cognitive domains. Secondly, a recent paper comprised of a combined sample of BD and schizophrenia (SZ) cases ($n = 73$) concluded that shorter telomere length was associated with being classified as cognitively impaired, however without specifying the cognitive domain (Gurvich et al., 2022). Moreover, only eleven of the participants in the study had a BD diagnosis. The studies above included a relatively small sample of patients with BD with limited information of cognitive correlates, hence larger studies are needed in BD investigating the role of telomere length and cognitive functioning.

In the case of BD, lithium use may also influence telomere length, as well as cognitive functioning. Long-term use of lithium is linked to longer telomere length (Powell et al., 2018; Pisanu et al., 2020), whereas the impact of antidepressants and antipsychotics on telomere length remains unclear (Powell et al., 2018). Studies of lithium have indicated a positive association between lithium use and performance on working memory and verbal memory tasks (Burdick et al., 2020). Accordingly, we examined telomere length and cognitive functioning in BD adjusted for medication use. We anticipated that shorter telomere length will be associated with poorer cognition, specifically verbal memory and learning adjusted for confounders.

2. Methods

2.1. Participants

The current study sample consists of a total of 647 participants (BD [$n = 246$] and HC [$n = 401$]). Clinical participants were recruited from psychiatric units of four major hospitals located throughout Oslo, as part of the large-scale TOP study. During this time, the participants had to have been under the care of mental health professionals. Controls were recruited utilizing a random selection method based on the population registers of Oslo and Akershus counties. Recruitment of all participants took place between 2007 and 2018. Sixty-five percent of the patients had a BD I diagnosis, 27 % had a BD II diagnosis, and 8 % a BD Not Otherwise Specified (NOS) diagnosis. The inclusion criteria for HC included: no current or lifetime diagnosis of a severe mental disorder based on the diagnostic and statistical manual of mental disorders-IV (DSM-IV) Williams, (First et al., 2002), as well as no substance use issues within the last 6 months. Exclusion criteria for all participants included age outside the 18–65 range, not being sufficiently fluent in Norwegian to undergo neuropsychological assessment and a current or past organic psychosis, neurological disorder or other medical condition which could impact cognitive functioning. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, with all participants providing written informed consent.

2.2. Clinical assessment

Participants were assessed using the Structured Clinical Interview for DSM-IV (Axis I disorders (SCID-I), chapters A-E; Spitzer et al., 1992). Clinicians conducting clinical assessment received regular clinical supervision from senior researchers and professors, both individually and in groups. Inter-rater reliability was assured by scoring a series of videos (Ventura et al., 1998) and a good inter-rater reliability for diagnostic assessments at the TOP study was indicated, with an overall kappa score between 0.92 and 0.99 across assessments (Høegh et al., 2020). In addition to clinical diagnoses, information was collected on the duration of illness (defined as current age minus age at onset of a first SCID verified episode), and a split version of the Global Assessment of Functioning Scale, GAF (Pedersen et al., 2007) was used to assess current symptomatology and functioning. Data on daily defined dose (DDD; WHO, 2018) and type of medication was collected through interviews and reviews of the participants' medical charts.

2.3. Cognitive Assessment

All participants underwent neuropsychological testing within 2 weeks of clinical assessment. Assessments were carried out by a clinical psychologist or psychology students, trained in standard neuropsychological assessment. Participants included prior to 2012 were tested using the cognitive test battery described by Simonsen et al. (Simonsen et al., 2010) (Battery 1), whilst participants enrolled after 2012 were examined using tests included in the new MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008) (Battery 2). Tests from both batteries measuring the same cognitive function were transformed to z scores and merged to form overarching cognitive domains. The z-scores were calculated based on the mean and the Standard Deviation of the healthy controls group. Table S1 illustrates the five established cognitive domains and the corresponding tests from each battery included in the current study. Case control differences in partly overlapping samples have been reported previously (Demmo et al., 2017; Simonsen et al., 2010), as well as presented in Supplementary S2.

2.4. Telomere length

Blood samples utilized for telomere length were usually collected within 2 weeks of clinical assessment. Telomere length was measured in peripheral blood leukocytes, utilizing a previously validated quantitative real-time polymerase chain reaction (qPCR) method (Aas et al., 2019). Briefly, 10 ng of DNA extracted from blood leukocytes was combined with 5 μl of SYBR®Green JumpStart Taq Ready Mix and 0.25 μl of ROX reference dye. The primers for the telomeric reaction included: 300 nM TelA (5′-CGG TTT GTT TGG GTT TGG GTT TGG GTT TGG GTT TGG GTT-3′) and 900 nM TelB (5′-GGC TTG CCT TAC CCT TAC CCT TAC CCT TAC CCT TAC CCT-3′) respectively. Moreover, the single copy gene 36B4 included primers 200 nM 36B4F (5′- CAG CAA GTG GGA AGG TGT AAT CC 3′) and 400 nM 36B4R (5′-CCC ATT CTA TCA ACG GGT ACA A-3′). All telomere length measurements were assessed using a 384-well plate Applied Biosystems 7900HT Fast Real Time qPCR. Three DNA samples with pre-measured telomere length (10.4 kb, 3.9 kb and 2 kb) were ran alongside the study batch to act as controls. Invalid samples, those in the top 5 % and bottom 5 %, were all re-evaluated. The results provided researchers with a telomere to single copy ratio (T/S ratio), which was used as an estimate of mean telomere length, with smaller T/S ratios being an indication of shorter mean telomere length. All blood samples were stored in The Biobank, located in Oslo, Norway. Analyses of variation coefficients revealed that the study sample possessed an intra-assay coefficient of 6.07 % and an inter-assay coefficient of 6.08 %.

2.5. Statistical analysis

Statistical analyses were performed using the IBM SPSS v26 software. Chi-Squared tests were run for all categorical variables (sex and ethnicity) investigating distributions across the two groups. Analysis of covariance (ANCOVA) was applied to investigate differences in telomere length in patients and controls adjusted for age, sex, and ethnicity (Europeans versus other). Due to skewed distribution, telomere lengths were log-transformed before being added into the parametric models. Linear regressions were used to analyze the relationship between telomere length and cognition in cases and controls separately, with each cognitive domain acting as the dependent variable, whilst telomere length was added as the independent variable. All analyses were adjusted for chronological age, sex, ethnicity. Analysis within cases were also adjusted for medication DDD. Assumptions for linear regression were checked and found satisfactory. The main analyses were adjusted for False Discovery Rate (FDR). As we anticipated shorter telomere length being associated with poorer verbal memory and learning correlates in BD, alpha level was set at 0.05 with FDR corrections.

For any significant group differences, Cohen's *d* was used to quantify effect sizes (Cohen, 1988; Durlak, 2009). Effect size measures were interpreted using Cohen's rules of thumb, where 0.20 represents a small effect, 0.50 a medium effect, and 0.80 a large effect size (Cohen, 1988; Durlak, 2009). Standardized coefficient betas are presented for the regression analysis. The standardized beta coefficient can be interpreted using similar guidelines to that of Cohen's *d* (Durlak, 2009).

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the study sample are provided in Table 1. There was no significant difference in age between the groups ($p > 0.1$). Patients with BD were more likely to be females and of non-European origin compared to the controls group. In terms of medication, 48.8 % of the BD sample was on any type of mood stabilizing or anticonvulsive medication (20.7 % on lithium), 52.8 % on any type of antipsychotic medication (8 % on first generation antipsychotics) and 25.2 % on antidepressant medication. Patients had a mean GAF function and symptoms score of 57.4 and 56.9, respectively, suggestive of moderate problems with functioning and symptom levels. No association was observed between medication DDD (both subtypes and total DDD) and telomere length, or current affective or psychotic symptoms and telomere length ($p > 0.1$). No difference in telomere length in lithium treated versus non lithium treated patients (see Supplementary Material S3). The association between telomere length and chronological age was on the threshold of statistical significance ($\beta = -0.07$, $p = 0.07$).

Table 1
Demographic overview of study sample.

Variable	BD (n = 246)	HC (n = 401)	Statistics	Post hoc analyses
Age (years), mean (SD)	31.85 (11.32)	31.39 (7.63)	F = 0.38, p = 0.538	–
Gender			$\chi^2 = 13.64$,	
Male, N (%)	102 (41.5)	227 (56.6)	p < 0.001	BD < HC
Ethnicity			$\chi^2 = 32.57$,	
European, N (%)	214 (87)	393 (98)	p < 0.001	BD < HC
Years of education, mean (SD)	14.50 (2.94)			
Duration of illness, mean (SD)	8.26 (8.97)	–	–	–
Psychopathology (GAF)				
Symptom, mean (SD)	56.93 (11.97)	–	–	–
Function, mean (SD)	57.41 (45.22)		–	
Mood stabiliser dose[a] (mg/day), mean (SD)	0.47 (0.62)	–	–	–
Antidepressant dose (mg/day), mean (SD)	0.43 (0.98)	–	–	–
Lithium dose (mg/day), mean (SD)	0.21 (0.48)	–	–	–
Antipsychotic dose (mg/day), mean (SD)	0.64 (1.48)	–	–	–
Telomere length (T/S ratio), mean (SD)	1.35 (0.63)	1.39 (0.46)	F = 6.45, p = 0.011	BD < HC

BD = Bipolar Disorders, HC = Healthy Controls, n = number, SD = standard deviation, mg/day = milligrams per day, T/S ratio = telomere to single copy gene ratio (values for statistics [F and p-value] are based on log transformation and adjusted for age, sex and ethnicity).

[a] Mood stabilizers including inconclusive medication.

3.2. Telomere Length and group status

Patients with a BD diagnosis had shorter telomere lengths compared to HC, adjusted for chronological age, sex, and ethnicity (Cohen's $d = 0.11$, $F = 6.45$, $p = 0.01$, see Fig. 1, Table 1). Moreover, there was no significant difference in telomere length between lithium treated vs. non-treated BD patients (see Supplementary Material, Table S4).

3.3. Telomere length and cognitive functioning

Telomere length was significantly associated with verbal learning in the BD sample both in adjusted and unadjusted models ($\beta = 0.14$, $p = 0.025$ & $\beta = 0.17$, $p = 0.009$; see Table 2, Fig. 2). Moreover, sensitivity analyses examining the impact of lithium, conducted by removing lithium treated patients from regression models, indicated that the relationship remained significant (see Supplementary Material, Table S3). In addition, telomere length was significantly associated with verbal memory in unadjusted models ($\beta = 0.14$, $p = 0.026$), however this association did not survive adjustment. No significant relationship was observed for telomere length and the remaining cognitive domains (working memory, executive functioning, or processing speed, all p's > 0.1). No association was observed for telomere length and cognitive functioning within the control sample, in both adjust and unadjusted models (see Supplementary Material, Table S5). Analyses were adjusted for chronological age, sex, ethnicity, and medication dose (DDD).

4. Discussion

We found shorter telomere length in patients with bipolar disorder (BD) than in healthy controls (HC). Within the patients, longer telomere length was associated with having better performance on verbal learning adjusted for demographic and clinical confounders. No other associations were observed for telomere length and cognitive functioning, thus the role of telomere length on the cognitive presentation in BD seems limited.

Our findings expand previous findings of telomere length and cognition in BD (Powell et al., 2018; Gurvich et al., 2022). Powell et al. (2018) reported shorter telomere length in patients with BD presenting with poorer verbal memory performances (Power et al., 2018), whilst in our study this association was only at a trend level. Our study was larger ($n = 246$) and included adjustments for confounders which was not reported in latter study. Furthermore, Powel et al. included a broader group of participants comprised of BD ($N = 63$), BD relatives ($N = 74$) and healthy controls ($N = 80$) whilst in the current study BD and in healthy individuals were analyzed separately. Our finding, and the findings by Powel et al., support a telomere length association with memory consolidation and memory storage rather than short-term memory; the current study strengthens these findings showing that it is specific to BD and not observed in healthy individuals. Another recent study included a transdiagnostic sample of both BD and SZ patients observed a negative relationship between telomere length cognitive

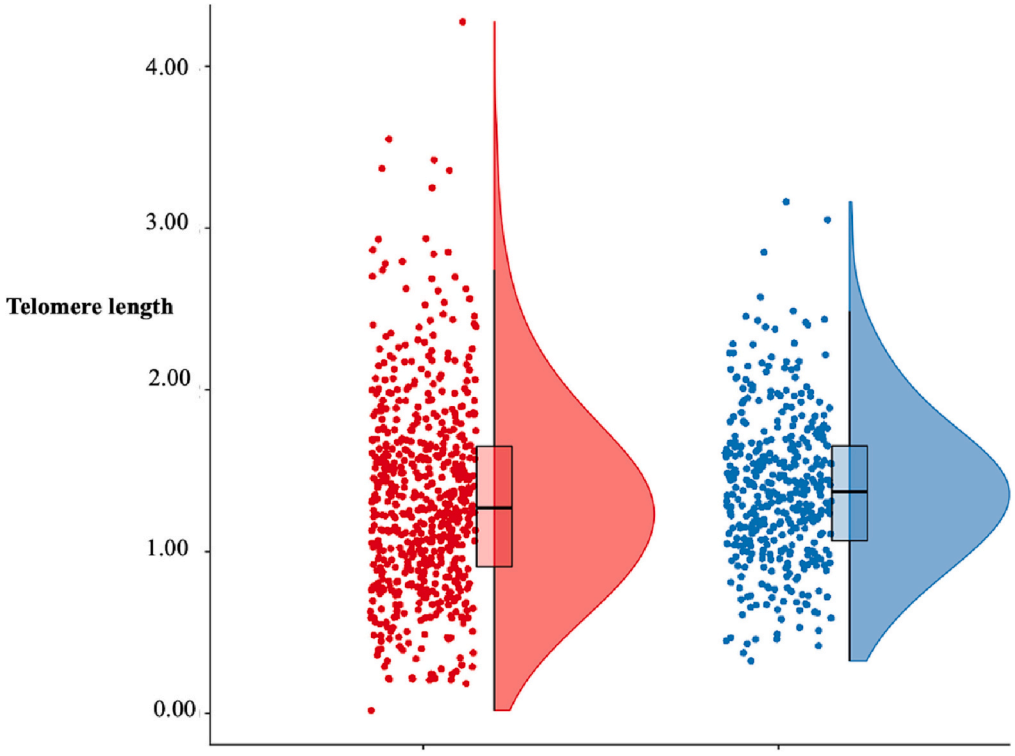

Fig. 1. Telomere length and case controls status.
ANCOVA, Cohen's $d = 0.11$, $F = 6.45$, $p = 0.01$. Data were adjusted for chronological age, sex, and ethnicity. Telomere length = Telomere length ratio. Patients had shorter telomere length ratio than controls.

Table 2
Telomere length and cognitive functioning in BD.

				95 % confidence intervals					95 % confidence intervals	
Dependent variable	Std. error	Beta[a]	Significance	Lower	Upper	Std. error	Beta[b]	Significance	Lower	Upper
Working memory	0.120	0.087	0.118	−0.078	0.396	0.121	0.083	0.212	−0.087	0.391
Verbal fluency	0.128	0.041	0.536	−0.173	0.331	0.127	0.025	0.704	−0.202	0.298
Processing speed	0.166	0.030	0.646	−0.250	0.402	0.154	−0.007	0.908	−0.322	0.286
Verbal memory	0.118	0.146	**0.026**	0.032	0.498	0.111	0.112	0.070	−0.016	0.422
Verbal learning	0.125	0.170	**0.009**	0.082	0.574	0.121	0.142	**0.025**	0.035	0.512

Linear regression. Bold numbers represent results which reached the threshold of statistical significance.
[a] Unadjusted.
[b] Adjusted for age, sex, ethnicity, and medication (daily defined dose).

functioning, however the cognitive area of impairment was not specified (Gurvich et al., 2022). It should be mentioned that the patients in the study by Powell et al. (2018) and Gurvich et al. (2022) had a mean age of 45 and 47, respectively, compared to 31 years in the current study. Hence, for older BD patients, the value of telomere shortening as an indicator of cognitive functioning could be compounded by the general age-related cognitive impairment effect on memory.

The area of telomere length and cognitive functioning in BD is currently understudied, however, similar findings have been reported in SZ (Czepielewski et al., 2018). Czepielewski and colleagues showed a positive correlation between telomere length and verbal memory, as well as a positive correlation between telomere length and grey matter volume in 48 patients with SZ. Czepielewski and colleagues concluded that accelerating ageing processes may be a mechanism behind cognitive impairments and grey matter reduction in SZ.

Shorter telomere length has been reported previously in BD populations and in their BD-unaffected relatives (Squassina et al., 2017), supporting accelerated cellular ageing as indexed by telomere length in BD. Shorter telomere length seems not be specific to BD as it is also observed in other severe mental disorders, including depression, SZ, and anxiety (Savolainen et al., 2012, Darrow et al., 2016; Vakonaki et al., 2018). Thus, accelerated ageing processes seem to be present across mental disorders and not only in BD. Intriguingly a large study of 1960 healthy men aged between 42 and 58 observed a negative relationship between telomere length and total grey matter volume, as well as areas of hippocampus, amygdala, and inferior temporal region (King et al., 2014). The association of telomere length and the size of the hippocampus and fusiform regions was stronger in individuals older than 50 years compared to younger individuals (King et al., 2014). As discussed by King and colleagues the structural changes associated with shortened telomere length may lead to an increased vulnerability to dementia and psychological disease. Cells in the brain that undergo cell division in adulthood (including microglia, astrocytes, oligodendrocytes, and pericytes) could be specifically vulnerable to detrimental effects of short telomeres. In mice, damage to pericytes leads to neuronal damage and neurofibrillary tangle deposition in the hippocampus and cerebral cortex (Sagare et al., 2013). Hence, telomere shortening is a plausible biological mechanism underlying accelerated ageing which is associated with changes in cognitive functioning, especially memory and the hippocampus, a brain area important for verbal learning and memory

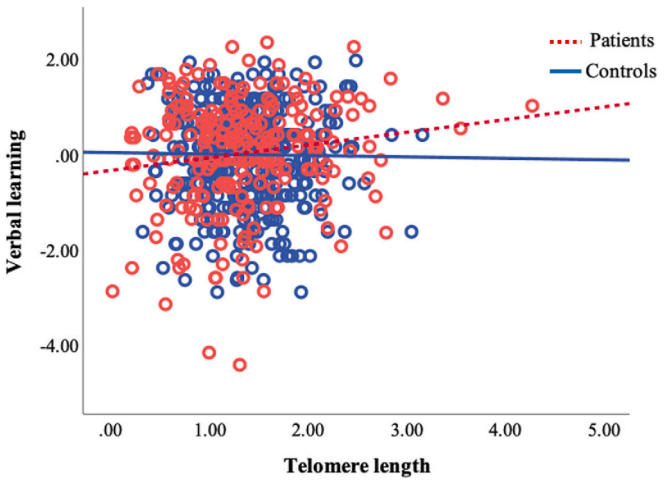

Fig. 2. Telomere length and verbal learning in bipolar disorders and in healthy controls.
Regression analyses. A positive association was observed between learning performance and telomere length within the patient's ($\beta = 0.14$, $p = 0.025$), but not the controls ($p > 1.0$). Data were adjusted for chronological age, sex, ethnicity, and lithium DDD. Telomere length = Telomere length ratio.

(Bonner-Jackson et al., 2015).

The study by King and colleagues further supports a stronger association of telomere length and reduction in grey matter volumes in individuals of age 50 and older compared to younger participants, suggesting that shorter telomere length may be more important when the normal effect of regular ageing start to appear. Our sample in the current study had a mean age of 30 and it could be argued that the participants were simply too young for any noticeable age-related cognitive decline. Although we found a nominal association between shorter telomere length and poorer performance on a learning task, it is important to note that our study does not support that the cognitive impairments observed in BD (Demmo et al., 2017; Simonsen et al., 2010) can be explained by shorter telomere length as an index of accelerated ageing. Thus, our study indicates that other factors may be involved in cognitive impairments in BD. Cognition is highly heritable (Mollon et al., 2021) and future studies should include genetic factors such as a polygenic risk score for cognition when disentangling the mechanism of cognitive impairments and biological ageing mechanisms in BD.

4.1. Strengths & limitations

A strength of the study is the inclusion of a large well-characterized clinical sample encompassing a total of 647 participants. Previous studies on telomere length and cognitive functioning in BD have been comprised of smaller samples ($N < 100$), with less detailed information on specific cognitive domains. As discussed briefly in the sample description, the clinical participants had to have been under the care of a mental health service, however information on psychosocial interventions are lacking. Whilst research on the topic has not indicated a change in telomere length based on psychotherapy exposure (Wang et al., 2017; Månsson et al., 2019), certain studies have noted an increase in telomerase activity post CBT (Månsson et al., 2019). Therefore, future studies should also focus on the impact that psychosocial support could have on the aetiology of telomere length in severe mental disorders, as well as it's impact on the relationship between telomere length and cognitive functioning. Moreover, another methodological limitation is the use of the qPCR in measuring TL. Whilst the qPCR is a validated method of measurement often employed in epidemiological research due to its ability to provide results using only a small sample of DNA (ng; Lindrose et al., 2021), the qPCR method measures the mean telomere length as opposed to the proportion or number of short telomeres within a sample (Aas et al., 2019). Therefore, a better overview of the relationship between shorter telomeres and cognition may have been achieved using a measurement technique with a higher sensitivity to short telomeres. As discussed in Birkenæs et al. (2021), the lack on an association between lithium use and telomere length could be explained by lack of statistical power as only 20.7 % of the patients were treated with lithium medication, as well as the duration of treatment was relatively short (less than two years, see Birkenæs et al., 2021 for more details).

Furthermore, as already mentioned, the participants in our study may have been too young (mean age 30 ± 9.20) to find a strong effect of telomere length on cognitive functioning. Supported by the large study by King et al. (2014), the effect may have been larger if we investigated older participants where ageing effects are prevalent. It should also be noted that our betas, effect sizes and *p*-values for the significant findings were weak and would not have survived a conservative Bonferroni adjustment, thus findings should be interpreted with caution. Based on the literature, we anticipated verbal memory and learning to be important cognitive components within this context, supporting a more lenient FDR multiple testing correction procedure for memory related analysis (comprised of verbal memory and learning).

To conclude, our study contributes to new knowledge on the field of telomere length and cognitive performance in BD. Whilst we observed evidence of shorter telomere length in BD compared to HC and poorer verbal learning correlates, the role of accelerated ageing on cognitive functioning in a relatively young group of patients with BD seems limited.

CRediT authorship contribution statement

Vid Mlakar and Monica Aas wrote the first draft. All authors have contributed to the manuscript and approved the final version.

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Declaration of competing interest

No conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.07.087.

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