

## Analyzing leukocyte telomere length in bipolar disorder: Authors' reply

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Our original study adds important information to the evidence base for bipolar disorder (BD) pathology. We show, for the first time, that shorter leukocyte telomere length (LTL) is already present in individuals with the early stages of BD and is comparable to LTL from individuals in the late stages of the disease.<sup>1</sup>

This result is at least surprising. We might speculate that, in BD, LTL would be proportional to disease duration. A recent study from our group in patients with schizophrenia (SZ) showed that duration of illness, but not age itself, is related to many markers of aging; these results are consistent with the hypothesis of accelerated aging induced by a pathological state.<sup>2</sup> Still, SZ is associated with a higher burden of disease. In our recent study, the similar LTL among early-stage and late-stage BD patients could indeed have many other explanations.

First, although hypertension, dyslipidemia, and diabetes mellitus are risk factors for telomere erosion and senescence, and were present in our cohort of BD patients, we chose not to report these data, because we have no information regarding comorbidity duration and its differential impact. Telomeres are naturally shortened during cell division and this process can be accelerated under oxidative, inflammatory or glucocorticoid stress, all of which are present in patients with BD. Importantly, augmented peripheral cell apoptosis, which may be a consequence of augmented turn-over secondary to chronic stress, has been reported in BD. Thus, during chronic stress, cells with shorter telomeres might have already been eliminated, selecting for medium to large telomeres. Second, quantification of telomere length by quantitative PCR (qPCR) provides a measure of the mean LTL present in a given cell population. A major limitation of this technique is its sensitivity, as qPCR does not detect short telomeres. Because short but not average LTL determines pathological phenotypes and drives cell fate, our results must be interpreted with caution.

In addition, LTL is a mosaic trait, and reflects the replicative history of the analyzed tissue. Granulocytes have longer telomeres than any other leukocyte subset and are present in higher numbers in BD patients. LTL from patients with late-stage BD could be enriched in the granulocyte population, leading to overestimation and misinterpretation of the real impact of LTL. Finally, we could also argue that similar LTL could be a consequence of pharmacotherapy. Lithium therapy is associated with neuroprotective properties.<sup>3</sup> This effect could explain why euthymic patients in late-stage BD under longer lithium therapy might have similar LTL to early-stage BD patients.

Two recently published reports from our group address telomere shortening and familial traits in BD<sup>4</sup> and SZ.<sup>5</sup> Our findings show a significant negative trend for shorter LTL among patients with BD when compared to their healthy siblings, and similar and shorter LTL among

patients with SZ and their unaffected siblings. More importantly, in both studies, LTL was shorter in unaffected siblings than in healthy nonrelated controls (HCs). Because HCs and unaffected siblings of BD patients had significant differences in LTL, we might speculate that telomere shortening is not influenced by medication and is indeed a neurobiological change with a clear genetic background. Furthermore, we might consider that genetic background in unaffected siblings could be seen as a susceptibility or vulnerability trait, and that resilience mechanisms may inhibit the appearance of pathological BD. In this study, we indeed failed to address important confounders, such as comorbidities, physical activity, smoking, and lifestyle factors. We also did not include data regarding familial history of major psychiatric disorders, nor did we quantify LTL in participants' parents.

Both of our studies had cross-sectional designs, thus precluding inference of any causal associations. Prospective epidemiological studies with adequately calculated sample sizes should be designed and conducted in newly diagnosed, therapy-naive BD patients to evaluate specific mechanisms potentially associated with lithium neuroprotection in telomere homeostasis.

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### Disclosure

The authors report no conflicts of interest.

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## BDNF Val66Met polymorphism and memory performance in older adults: the Met carrier effect is more complex than previously thought

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Brain-derived neurotrophic factor (BDNF) is an important nerve growth factor linked with development and neural plasticity. The Val66Met polymorphism in the *BDNF* gene has been associated with a significant impact on episodic memory in adults. Azeredo et al.<sup>1</sup> investigated effects of the *BDNF* Val66Met polymorphism on memory performance. Their conclusion was that, in a sample of elderly adults, *BDNF* Met allele carriers had impaired episodic memory performance as compared to Val/Val homozygotes.<sup>1</sup> However, conflicting evidence to this report exists, and the correlation between memory and Met allele carrier status is quite complex. One previous report focusing on older adults suggested that the *BDNF* Met allele is associated with higher memory performance,<sup>2</sup> whereas other studies found no effect of *BDNF* Val66Met variant on memory in older<sup>3</sup> or young adults.<sup>4</sup> It is important to note that the effects of the Val66Met polymorphism are due to modification of BDNF synthesis. Azeredo et al. measured *BDNF* genotype, but not BDNF concentrations. Interestingly, Val66Met polymorphism has been shown to be associated with increased BDNF levels by Zhang et al.,<sup>5</sup> vs. the BDNF reduction presumed by Azeredo et al., where aging-related memory decline is possibly explained by reduced neurotrophin synthesis. Another limitation of this study was the failure to exclude psychiatric patients.<sup>1</sup> The BDNF increase noted in the study by Zhang et al. was demonstrated in patients with post-traumatic stress disorder, a condition known to have significant impact on memory.

In conclusion, we believe further research into the impact of *BDNF* genotype on memory should include measurement of BDNF levels as well as psychiatric screening for conditions likely to impact memory function.

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## BDNF Val66Met polymorphism and memory performance in older adults: the Met carrier effect is more complex than previously thought: Authors' reply

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Genetic association studies have presented inconsistent findings regarding the effects of the functional *BDNF* Val66Met polymorphism and cognitive function in healthy subjects and psychiatric patients, with heterogeneity in effect sizes across studies.<sup>1-4</sup> As these candidate gene studies have employed relatively small samples, it is difficult to interpret discrepant findings, which are the norm in genetic association research. By aggregating data across studies, meta-analyses provide a systematic method of evaluating such discrepant findings, as regarding the association between *BDNF* Val66Met polymorphism and memory function. In this context, a recently published meta-analysis estimated the effect of the *BDNF* Val66Met polymorphism on declarative memory tasks in 5,922 subjects, as well as on hippocampal grey matter volume in 2,985 subjects and on task-related change in hippocampal response measured by functional magnetic resonance imaging (fMRI) in 362 subjects.<sup>5</sup> The authors of this meta-analysis found evidence that declarative memory performance, hippocampal volume, and hippocampal activation are all reduced in *BDNF* Met allele carriers in comparison to Val/Val homozygotes. In our study, we examined the effect of the *BDNF* Val66Met polymorphism on declarative memory performance in a sample of 87 older adults recruited by convenience among community-based elders in Porto Alegre, Brazil. Our analysis yielded further evidence on the genetic contribution of the *BDNF* Val66Met polymorphism in memory performance, demonstrating that *BDNF* Met allele carriers had lower delayed verbal recall and a decline in memory retention as compared to Val/Val homozygotes. Although our findings provided additional evidence of an



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