association between the BDNF Val66Met polymorphism and memory, we have no such evidence regarding peripheral levels of BDNF. In fact, the BDNF Val66Met SNP does not affect plasma BDNF levels, as pointed out in recent research.6,7 Therefore, unlike Drs. Lipov and Candido, we do not consider the lack of peripheral BNDF measurement a limitation of our study. Nevertheless, we agree that, to better understand the dynamics of the BDNF changes demonstrated in our study, novel approaches to measurement of levels of the corresponding proteins are necessary.

Although candidate gene studies have linked the BDNF Val66Met polymorphism with posttraumatic stress disorder (PTSD), a recent meta-analysis did not find a significant overall effect of this SNP on susceptibility to PTSD.8 On the other hand, subgroup analyses suggested that the stress status of the control group could affect the relationship between the BDNF Val66Met polymorphism and PTSD risk. Considering the heterogeneity of findings associating this polymorphism with cognitive performance in elderly adults, our study was designed to investigate the effects of this genetic variant on declarative memory performance specifically in this population. Considering that the percentage of older adults with PTSD is around 3%,9 the overall impact of this diagnosis in our sample is probably negligible.

Lucas A. Azeredo, Tatiana De Nardi, Rodrigo Grassi-Oliveira
Developmental Cognitive Neuroscience Lab (DCNL), Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil. Inscer – Instituto do Cérebro, PUCRS, Porto Alegre, RS, Brazil
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Biomarkers in first-degree relatives of patients with bipolar disorder: what can they tell us?
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The study of subjects at increased risk of bipolar disorder (BD), such as first-degree relatives of patients, is a highly relevant and informative approach for investigation of the mechanisms involved in BD risk and onset. Because biological siblings of patients with BD, for example, share part of their genetic background with the latter, they are likely to present at least a subset of genetic markers of BD susceptibility. Although the reported heritability of BD is extremely high (70-80%), recent studies have suggested that its multifactorial molecular genetics is determined by several common and rare genetic variants, each with very small penetrance.1 Whether these risk markers will lead to onset of illness in susceptible subjects is likely determined by a combination of numerous factors, particularly environmental exposures.

The study by Nery et al.2 recently published in Revista Brasileira de Psiquiatria was the first to examine peripheral brain-derived neurotrophic factor (BDNF) levels in unaffected siblings of patients with BD. Their ultimate goal was to investigate whether abnormal expression of this neurotrophin might represent an endophenotype of illness, i.e., a quantitative trait that is intermediate between the disease phenotype and its underlying biological process.3 Despite their negative results, the study makes use of a clinically well-characterized sample and provides evidence that, contrary to the initial hypothesis, a high genetic risk is not accompanied by altered peripheral BDNF levels in unaffected siblings of patients with BD. This finding was recently replicated in another population of high-risk siblings.4

The concept and investigation of endophenotypes has emerged as a strategy to overcome methodological difficulties inherent to the classical investigation of complex heterogeneous disorders, such as BD. The traditional definition of endophenotypes states that: i) they should be associated with the illness in the population; ii) they should be heritable and state-independent (i.e., detectable regardless of whether the illness is active); iii) they should co-segregate within families; and iv) they should be detectable in unaffected relatives of patients at a higher rate than in the general population.5 Because of
this, first-degree relatives represent an invaluable population for endophenotype research. In addition, endophenotype-oriented studies of psychiatric disorders are particularly supported by the Research Domains Criteria (RDoC), which has been recently proposed by the National Institute of Mental Health as an alternative to current research approaches.

Finally, the study of first-degree relatives also provides an ideal framework for analysis of the risk/resilience diathesis, considering that their genetic background has been shown to lead to a 10- to 20-fold increased risk of developing BD compared with relatives of healthy individuals. Longitudinal assessments of these individuals through the ages of peak risk of illness onset (15-24 and 45-54 years) are particularly warranted, and should not only allow identification of biomarkers and/or environmental factors associated with resilience to BD, but can also provide predictive measures or pinpoint the most relevant prodromal symptoms for those that will ultimately develop a full-blown psychiatric diagnosis.

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Psychosis: glia, immunity, and melatonin

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I read with interest the recent article by Duarte et al. reviewing the neurobiological underpinnings of bipolar disorder (BD).\(^1\) Such work is part of a growing body of interest on the role of not only glia, but wider immunity, alterations in psychosis.\(^2\) This places the regulation of immune responses as an important target in the pathophysiology of schizophrenia and BD. In this context, it should be noted that melatonin plays an important role in the regulation of both immune and glial cell reactivity, including through its autocrine effects, which world-leading work by Markus et al. in Brazil has shown.\(^3\)

Melatonin is classically associated with night-time release by the pineal gland and thereby with the regulation of the circadian rhythm. However, a plethora of recent data shows that melatonin is synthesized in many, if not all, mitochondria-containing cells.\(^2\) As such, the genetic associations of melatonin with BD are likely to be linked to changes in a wide array of organs and tissues, including the gut, as well as in glia and immune cell regulation. Likewise, the general decrease in pineal melatonin levels in schizophrenia is likely to represent alterations in central and peripheral sites, as well as in circadian regulation.

Given that melatonin may decrease the levels of metabolic dysregulation induced by mood stabilizers and antipsychotics, its immediate clinical utility in psychosis should be highlighted.

However, the targeting of local melatonin synthesis in glia and immune cells is now a significant pharmaceutical company target. The recent development of alpha-7 nicotinic receptor agonists as cognitive enhancers in schizophrenia, as well as in Alzheimer’s disease, may also require the careful regulation of melatonin synthesis, given that melatonin regulates the levels and activity of this nicotinic receptor, again as shown by Markus et al.\(^4\) The alpha-7 nicotinic receptor is also a significant inhibitor of glial and immune cell reactivity, suggesting that its interaction with levels of melatonin is likely to modulate its clinical utility.

Most general practitioners and psychiatrists have an underappreciation of such wider roles of melatonin, and of its clinical utility across a host of psychiatric and other medical conditions. It is not unlikely that the pathophysiological changes underpinning the data...