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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.¹ 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.¹ 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,² whereas other studies found no effect of *BDNF* Val66Met variant on memory in older³ or young adults.⁴ 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.,⁵ 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.¹ 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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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: 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.¹⁻⁴ 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.⁵ 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

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 BDNF 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.

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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.³ Because of