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Disturbances in selective information processing associated with the BDNF Val66Met polymorphism: Evidence from cognition, the P300 and fronto-hippocampal systems

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ABSTRACT

In this study, we examined whether the Met allele of the BDNF Val66Met polymorphism is associated with selective disruptions to task-relevant information processing. In 475 non-clinical participants for whom BDNF genotype status was determined we used the 'IntegNeuro' computerized battery of neuropsychological tests to assess cognitive performance, an auditory oddball task to elicit the P300 event-related potential (ERP) and, in smaller subsets of these subjects, high resolution structural MRI imaging to quantify fronto-hippocampal grey matter ($n = 161$), and functional magnetic resonance imaging to assess fronto-hippocampal BOLD activation ($n = 37$). Met/Met (MM) homozygotes had higher verbal recall errors, in the absence of differences in attention, executive function, verbal ability or sensorimotor function. Further, MM homozygotes demonstrated a slowed P300 ERP during the oddball task, with corresponding alterations in hippocampal and lateral prefrontal activation, and a localized reduction in hippocampal grey matter. These results are consistent with a subtle impact of the Met allele on fronto-hippocampal systems involved in selective information processing of stimulus context and memory updating within the normal population. The findings also indicate that heritable endophenotypes such as the P300 have value in elucidating genotype–phenotype relationships.

Functional brain imaging provides a powerful approach for investigating functional genomics because it can more directly capture the effects of genetic variation on information processing than behavioral measures (Hariri and Weinberger, 2003). Highly heritable measures, such as the P300 event-related potential (ERP), have already shown promise as brain imaging endophenotypes in studies of several clinical disorders (Bramon et al., 2005; Hesselbrock et al., 2001), while functional magnetic resonance imaging studies reveal variations in neural activity with cognition, in the absence of behavioral differences (Hariri and Weinberger, 2003).

Brain derived neurotrophic factor (BDNF) is a key neurotrophin involved in cell survival and context-dependent synaptic plasticity, and has been implicated in selective information processing relevant to learning and memory. BDNF is synthesized as pro-peptide and is cleaved intracellularly to release mature, secreted growth factor that selectively binds to members of the *Trk* family of receptor tyrosine kinases that promote survival and differentiation (Friedman and Greene, 1999). These synaptic changes have been demonstrated in a variety of cellular models, such as hippocampal long-term potentiation (LTP), and are associated with learning and adaptive behaviors in animals (Poo, 2001; Tyler et al., 2001).

Within the BDNF gene, a distinct haplotype containing a frequent single nucleotide polymorphism (SNP), located at nucleotide 196 (dbSNP rs6265), results in a valine to methionine (Val66Met) substitution in the pro-peptide of the BDNF molecule.

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As a result, the BDNF methionine-containing variant (Met) fails to localize to secretory granules or synapses, resulting in inefficient activity-dependent secretion (Chen et al., 2004; Egan et al., 2003). The BDNF Met allele has been associated with a wide range of psychiatric and neurodegenerative disorders, which involve a loss of neuronal integrity, including Alzheimer's disease (Kunugi et al., 2001; Riemenschneider et al., 2002; Ventriglia et al., 2002), Parkinson's disease (Momose et al., 2002), bipolar disorder (Neves-Pereira et al., 2002; Sklar et al., 2002), neuroticism as a vulnerability trait for depression (Sen et al., 2003), anorexia nervosa (Ribases et al., 2003) and obsessive-compulsive disorder (Hall et al., 2003).

In addition to associations with various neuropsychiatric disorders, Met/Met (MM) homozygosity has been associated with cognitive impairments in otherwise healthy individuals. Impairments in episodic memory combined with exaggerated hippocampal function during an fMRI working memory task have been found (Egan et al., 2003). Differences in hippocampal function have also been observed in Met carriers during a declarative memory task (Hariri et al., 2003). Structural brain differences are also evident, with the BDNF Met allele being associated with reductions in the hippocampus and dorsolateral prefrontal cortex, regions responsible for memory and attention (Bueller et al., 2006; Pezawas et al., 2004; Szeszko et al., 2005).

To date, few studies have examined the specificity of BDNF effects on memory in contrast to other cognitive domains. One study of elderly individuals reported better non-verbal reasoning in BDNF MM homozygotes, which was also reflected in their childhood scores from a 1932 survey (Harris et al., 2006), suggesting that BDNF Val66Met may impact other domains of cognition in adulthood. The BDNF polymorphism has also not been examined in relation to highly heritable cognitive brain function endophenotypes, such as the P300 ERP (O'Connor et al., 1994).

In this study, we employed the auditory oddball task to elicit selective information processing. The P300 (also known as 'P3b') elicited by a standard two-tone oddball task reflects voluntary detection of task-relevant, salient stimuli and has been associated with both regional neural inhibition involved in processing expected stimuli and the updating of activity in corticolimbic circuits during attention and working memory (Donchin and Coles, 1998; Polich, 2003; Soltani and Knight, 2000; Verleger, 1998). Biophysical modeling also implicates corticothalamo-limbic feedback in generation of the P300 (Rennie et al., 2002). These concepts of selective attention and context updating are relevant to evidence for the involvement of the BDNF polymorphism in aspects of learning and memory (Egan et al., 2003; Poo, 2001; Tyler et al., 2001).

Oddball stimuli have been found to elicit hippocampal activation in both intracranial P300 recordings (Halgren et al., 1980; Heit et al., 1990; McCarthy et al., 1989) and functional magnetic resonance imaging (fMRI) (Crottaz-Herbette et al., 2005; Kiehl et al., 2001; Williams et al., 2007; Yoshiura et al., 1999). However, there is also contrary evidence of P300 preservation despite unilateral hippocampal lesions (Jonson, 1989; Rugg et al., 1991). Moreover, infarctions of the posterior hippocampus, as well as anterior and medial temporal lesions, may induce P300 deficits over temporal as well as frontal sites (Knight, 1996; McCarthy et al., 1989; Onofrj et al., 1992). While hippocampal activation has been observed in the context of both frontal and parietal activation in the oddball task (e.g., Williams et al., 2007), other fMRI studies have observed distributed cortical activation in the absence of hippocampal engagement (e.g., Downar et al., 2002; Menon et al., 1997; McCarthy et al., 1997). Variation in hippocampal activation in these studies might in part reflect task and methodological variation.

Here we sought to determine whether the BDNF polymorphism shows specific associations with the memory domain of cognitive function, and whether BDNF variants are associated with disruptions to the P300 and underlying hippocampal–prefrontal networks (as measured by fMRI), in the same cohort of non-clinical individuals.

1. Methods

1.1. Subjects

A total of 475 participants (51% females, mean age of 32.4 ± 12.7 years) provided voluntary and informed written consent, according to the relevant local human research ethics committee, to participate in testing and the Brain Resource International Database (BRID; Gordon et al., 2005). To achieve a representative community sample, recruitment was undertaken professionally via widespread advertisement. Participants older than 60 years were excluded, given evidence that BDNF Val66Met genotypes might have differential effects on cognition in older age (Harris et al., 2006). Additional exclusion criteria were determined using the BRID personal history and screening assessments, which include the SPHERES (Hickie et al., 1998) and Patient Health Questionnaire (PHQ9) (Kroenke and Spitzer, 2002) to screen

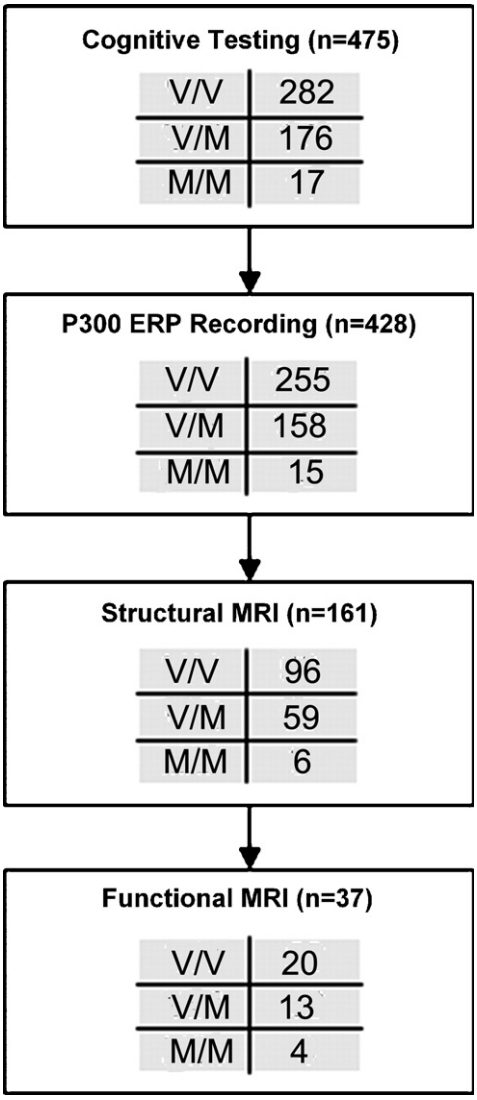

Fig. 1. A flow chart summarizing the distribution of BDNF Val66Met genotypes in the total sample, and in the subsamples for which ERP, MRI and functional MRI data were available. Importantly, each subsample was a subset of the total sample, and of each other (for instance, the functional MRI subsample was a subset of those completing MRI, ERPs and cognition). These subsamples were also matched in demographic factors to the total sample, such that the mean age, years of education and estimated IQ were the same (within one decimal place) within each subsample.