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The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly

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Abstract

In this study we examined the relevance of the functional brain-derived neurotrophic factor (BDNF) Val66Met polymorphism as a modulator of task-switching performance in healthy elderly by using behavioral and event-related potential (ERP) measures. Task switching was examined in a cue-based and a memory-based paradigm. Val/Val carriers were generally slower, showed enhanced reaction time variability and higher error rates, particularly during memory-based task switching than the Met-allele individuals. On a neurophysiological level these dissociative effects were reflected by variations in the N2 and P3 ERP components. The task switch-related N2 was increased while the P3 was decreased in Met-allele carriers, while the Val/Val genotype group revealed the opposite pattern of results. In cue-based task-switching no behavioral and ERP differences were seen between the genotypes. These data suggest that superior memory-based task-switching performance in elderly Met-allele carriers may emerge due to more efficient response selection processes. The results implicate that under special circumstances the Met-allele renders cognitive processes more efficient than the Val/Val genotype in healthy elderly, corroborating recent findings in young subjects.

Keywords: Aging; BDNF Val66Met polymorphism; Task switching; Response selection; Inhibition; Memory; Event-related potentials; Genetic imaging; N2; P3

1. Introduction

There is strong interindividual variability in cognitive performance in elderly (Hultsch et al., 2002). The question which factors determine these larger interindividual differences is of high importance in aging research. In this respect, the examination of genetic factors in close relation to neurophysiological and cognitive processes may be useful explaining the strong interindividual variability in cognitive performance.

During aging there is a decrease in secretion of the brain-derived neurotrophic factor (BDNF) affecting different cognitive functions (Hayashi et al., 2001; Pang and Lu, 2004). However, molecular genetic studies investigating the relevance of the functional BDNF Val66Met polymorphism (rs6265) for cognitive functions in elderly revealed contradictory results: some results accounted for compromised cognitive functions in Met-allele carriers (Miyajima et al., 2008) while other results accounted for better cognitive functions in Met-allele carriers (Erickson et al., 2008; Matsushita et al., 2005; Ventriglia et al., 2002). The study by Erickson et al. (2008) suggests that at younger ages the Val/Val homozygotes provide some neuronal and cognitive benefits but with increasing age they are associated with cognitive impairment, whereas the Val/Met carriers provide some protection against cognitive declines in older age (Harris et al., 2006).

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Variations in the functional BDNF Val66Met polymorphism modulate functions mediated by basal ganglia-prefrontal loops (e.g., Beste et al., 2010a, 2010c). These loops may be of special interest in elderly, as these are affected by aging processes (e.g., Beste et al., 2009, 2010b; Wild-Wall et al., 2008; Buckner, 2004). However, even though the ability to flexibly switch between different tasks is mediated via basal ganglia-prefrontal loops (Chudasama and Robbins, 2006; Kehagia et al., 2010); most existing studies on task switching in elderly showed impairments in maintenance of task goals, but not disturbed task-set switching performance (switch costs) in older versus younger participants (e.g., Kramer et al., 1999; Kray, 2006; Kray and Lindenberger, 2000; West and Travers, 2008). There are different theoretical accounts of switch costs, i.e., longer processing times when participants switched between cognitive tasks rather than repeating the same task. Switch costs may represent an additional active reconfiguration process (Monsell, 2003; Rogers and Monsell, 1995). This dynamic reconfiguration process may involve shifting attention between perceptual and conceptual elements, retrieving goals and condition-action rules from working memory or activation of relevant task sets and inhibition of irrelevant task sets (Kiesel et al., 2010; Monsell, 2003). An alternative account explained switch costs in terms of interference from the previous trial (task-set inertia) (Allport and Wylie, 2000; Allport et al., 1994).

As outlined above, aging selectively impairs some of the functions involved in task switching: whereas differentiating and updating of internal control settings seems to decline with decreasing age, small age-related changes were found for the task-set interference (e.g., Cepeda et al., 2001). However, age related impairments are often undetected when tasks are too easy, or performance declines are compensated by strategies. These strategies of elderly to compensate switch costs can be overcome by enhancing working memory load by means of memory-based task switching (Kray, 2006). As BDNF plays a pivotal role in working memory processes (Matsushita et al., 2005; Ventriglia et al., 2002), a task-switching paradigm in which working-memory load is varied seems well-suited to examine the relevance of the BDNF Val66Met polymorphism for cognitive control processes in elderly.

In the last decade processes underlying switch costs has been often related to event-related potentials (ERPs). Behavioral switch costs seem to be closely related to a frontocentrally distributed ERP component, the N2 reflecting the resolution of conflict (or task-set inertia) between simultaneously active stimulus-response mappings during response selection (Gajewski et al., 2010a). Besides the N2, task switching is related to a smaller P3b likely reflecting increased working memory load or stronger involvement of cognitive resources during implementation of a switching task-set (Barceló et al., 2000; Gajewski et al., 2010b; Gehring et al., 2003; Jost et al., 2008; Karayanidis et al., 2003; Kieffaber and Hetrick, 2005; Lorist et al., 2000; Poulsen et al., 2005). Thus, an efficient processing of a switching task would include an increased N2 and decreased P3 in the target-locked ERPs compared with the nonswitch trials.

With respect to findings suggesting superior cognitive performance in elderly Met-allele than Val-Val-allele carriers (Erickson et al., 2008), we expect better switching performance (i.e., lower switch costs and lower variability) in the Met-than the Val/Val group. The difference in switching costs between the genotypes should be particularly evident under high working memory load, i.e., when switching is memory based compared with a cue-based condition. Due to the relation of the N2 to overt performance (e.g., Beste et al., 2008; Gajewski et al., 2008, 2010a; Hohnsbein et al., 1998) we hypothesize an enhanced and/or faster N2 in Met allele carriers is related to lower switching costs in memory-based task switching. As the smaller P3b seems to go hand in hand with an increased N2, the reduction of the P3b in switch, compared with nonswitch trials is also stronger in Met-allele than in Val/Val genotype carriers.

2. Methods

2.1. Participants

One hundred thirty-one healthy volunteers aged from 65 to 88 (mean = 70.5, SD = 4.5) participated in the study. Eighty-one (61.8%) of them were female. Eleven participants were left- or ambidexter. They had normal or corrected-to-normal vision and gave informed consent for participation. All participants received a payment for their participation. The sample consisted of 79 subjects carrying the Val/Val genotype, 47 carrying the Val/Met genotype and 5 subjects carrying the Met/Met genotype group. The distribution of genotypes in the sample did not differ from Hardy-Weinberg equilibrium ($p = 0.537$), as determined using the program Finetti provided as an online source (ihg.gsf.de/cgi-bin/hw/hwa1.pl; T.F. Wienker and T.M. Strom). As to the expected low frequency of the Met/Met genotype group, the Val/Met and Met/Met genotype group were combined to 1 group (i.e., Val/Met-Met/Met genotype group). With respect to the frequencies reported in HapMap data for European populations, one would expect approximately 88 Val/Val genotypes, approximately 37 Val/Met genotypes, and approximately 4 Met/Met genotypes. The frequency of genotypes is therefore well in line with the frequency one would expect on HapMap data.

Fifty-eight participants of the Val/Val genotype (age mean = 70.8, SD = 4.7; Mini Mental State Examination [MMSE] = 28.3), were female (73.4%, $\chi^2 = 17.3$, $p < .0001$) and 23 of the combined Val/Met and Met/Met genotype group (age mean = 70.2, SD = 4.3; MMSE = 28.7), were female (44.2%, $\chi^2 = 0.7$, $p = 0.4$). The subgroups did not significantly differ regarding a number of neuropsychological and psychiatric parameters (Table 1).