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Research Report

The Met-genotype of the BDNF Val66Met polymorphism is associated with reduced Stroop interference in elderly

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ABSTRACT

Aging is accompanied by impairments of executive functions that rely on the functional integrity of fronto-striatal networks. This integrity is modulated by the release of neurotrophins like the brain-derived-neurotrophic factor (BDNF). Here, we investigate effects of the functional BDNF Val66Met polymorphism on interference processing in 131 healthy elderly subjects using event-related potentials (ERPs). In a Stroop task, participants had to indicate the name or the colour of colour-words while colour was either compatible or incompatible with the name. We show that susceptibility to Stroop-interference is affected by the BDNF Val66Met polymorphism: the Met-allele carriers showed better performance and enhanced N450 in interference trials. Other processes necessary to prepare and allocate cognitive resources to a particular task were not affected by BDNF Val66Met polymorphism, underlining the specificity of the observed effects. The observed performance and ERP difference is possibly due to dopamine related effects of BDNF in fronto-striatal networks, where it putatively mediates a shift in the balance of the direct and indirect pathway involved in inhibitory functions.

1. Introduction

Molecular genetic techniques are increasingly recognized as important tools to elucidate neurobiological determinants of human cognitive function (van Thriel et al., 2012). They may also prove useful to understand the large inter-individual differences in cognitive functions in aging (Harris & Deary, 2011; Hultsch & MacDonald, 2004; Lindenberger et al., 2008). Particularly, executive functions relying on the functional integrity of prefrontal networks are most affected in aging (MacDonald, Nyberg, & Bäckman, 2006). This neuronal integrity is modulated by neurotrophins like the brain-derived-neurotrophic factor (BDNF), which regulates survival, growth, maintenance and genesis of neurons (McAllister, Katz, & Lo, 1999; Pezawas et al., 2004). BDNF also regulates activity-dependent changes in synaptic plasticity, such as long-term potentiation (LTP) in the hippocampus (Bekinschtein et al., 2008; Egan et al., 2003). A common single nucleotide polymorphism (SNP) in the human BDNF gene (Val66Met; rs6265) leads to a valine (Val)/methionine (Met) substitution in the pro-domain of the encoded protein (Chen et al., 2004). The functional polymorphism alters the intracellular tracking and packaging of pro-BDNF, affecting the secretion of mature peptide (Egan et al., 2003). As compared to the Met-allele, the Val-allele is associated with higher activity of the BDNF system (e.g., Rybakowski, 2008), which linearly relates to increased neural activity (Kafitz, Rose, Thoenen, & Konnerth, 1999).

Association studies on the BDNF Val66Met polymorphism have revealed contradictory effects on cognitive functions, which may be also due to the variability of BDNF isoforms and the diversity of transcripts in different brain areas (Mandelman & Grigorenko, 2012). Specific memory functions are compromised in Met-allele carriers (episodic memory: Dempster et al., 2005; Egan et al., 2003; Li et al., 2010, declarative memory: Hariri et al., 2003) see also Miyajima et al., 2008 and Raz et al., 2009, but a number of studies found no association between BDNF and memory performance in different populations (Houlihan et al., 2009; Nacmias et al., 2004; Strauss et al., 2004; van Wingen et al., 2010; see also Mandelman & Grigorenko, 2012 and Payton, 2009, for an overview). While Mandelman and Grigorenko (2012) did also not detect a consistent association between BDNF and executive control processes, several recent studies showed that some executive functions are more efficient in Met-allele carriers (Beste, Baune, Domschke, Falkenstein, & Konrad, 2010a; Beste et al., 2010b) and particularly so in older subjects (Erickson et al., 2008; Foltynie et al., 2005; Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2011; Harris et al., 2006; Matsushita et al., 2005; Ventriglia et al., 2002). In elderly individuals, the relevance of the BDNF Val66Met polymorphism as a modulator of cognitive functions is even more salient than in young subjects, since cognitive processes move away from their optimum (Lindenberger et al., 2008; Nagel

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et al., 2008). Moreover, it has been shown that BDNF secretion is decreased in aging (Hayashi, Mistunaga, Ohira, & Shimizu, 2001; Pang & Lu, 2004).

We aimed at providing a further test for the hypothesis that the Met allele of the BDNF Val66Met polymorphism is associated with enhanced executive control processes in healthy elderly. We do so by means of event-related potentials (ERPs) in a healthy elderly cohort using a computerised version of the Stroop paradigm. Processes related to interference control have repeatedly been shown to depend on anterior cingulate and dorsolateral prefrontal areas (Beste, Domschke, Falkenstein, & Konrad, 2010c; Beste, Baune, Domschke, Falkenstein, & Konrad, 2010e; Liotti, Woldorff, Perez, & Mayberg, 2000; West, 2003). These areas are part of fronto-striatal loops (Chudasama & Robbins, 2006; Foltynie et al., 2005) known to play a crucial role in executive functions like response inhibition and response selection (Beste et al., 2012; Gajewski, Stoerig, & Falkenstein, 2008; Gajewski et al., 2011; Mostovsky & Simmonds, 2008; Paus, 2001; Picard & Strick, 1996; Turken & Swick, 1999). Inhibitory processes have generally been suggested to be crucial for interference control (Friedman & Miyake, 2004; Kok, 1999; Zysset, Müller, Lohmann, & von Cramon, 2001) and also for processing of incompatible Stroop responses (i.e., when the dominant task dimension (word reading) has to be suppressed) (Cohen, Dunbar, & McClelland, 1990; Cohen & Servan-Schreiber, 1992; Stroop, 1935; West & Alain, 2000).

Using ERPs it has been shown that incompatible Stroop stimuli evoke a centro-parietal negativity about 450 ms post-stimulus (Mager et al., 2007; Rebai, Bernard, & Lannou, 1997; West, 2003; West & Alain, 1999, 2000; West, Jakubek, Wymbs, Perry, & Moore, 2005), which is most likely generated by areas in the anterior cingulate cortex (ACC; Liotti et al., 2000; Markela-Lerenc et al., 2004) with a posterior shift for manual responses (Atkinson, Drysdale, & Fulham, 2003; Liotti et al., 2000; West, 2004) which suggests different sources within the ACC. The N450 reflects response, but not stimulus interference (Chen, Bailey, Tiernan, & West, 2011) and has consistently been associated with response conflict interference control induced by incompatible Stroop stimuli (Coderre, Conklin, & van Heuven, 2011; Liotti et al., 2000; West et al., 2005; West, 2004). Paralleling the increase of Stroop interference in elderly, this negativity has been shown to be attenuated in aging (Mager et al., 2007; West, 2004; West & Allain, 2000). This suggests that an attenuated negativity in incompatible trials is related to compromised interference control.

If the Met genotype confers a benefit to its carriers in executive control processes, we expect Met-allele carriers to show weaker interference effects on a behavioural level, as compared to Val/Val-allele carriers. This may be expressed in shorter reaction times (RTs), lower intra-individual variability of speed and lower error rates in Met-allele carriers, compared to Val/Val genotype carriers (cf. Gajewski et al., 2011; Getzmann et al. in press). On a neurophysiological level we expect that the central negativity, the N450, indicating successful interference control is attenuated in Val/Val genotype carriers, compared to Met-allele carriers. Moreover, in tasks imposing high demands on cognitive control the allocation of processing resources is essential (Freude & Ullsperger, 2000). These preparatory processes are reflected in the contingent negative variation (CNV; Falkenstein, Hoormann, Hohnsbein, & Kleinsorge, 2003; Walter, Cooper, Aldridge, McCallum, & Winter, 1964). As such, possible differences between elderly Met-allele and Val/Val genotype carriers in interference control may only be a side effect of more efficient preparatory processes that allocate processing resources to the task-relevant cognitive process. If this is the case, the CNV should be enhanced in elderly Met-allele carriers, compared to Val/Val genotype carriers, and particularly so in conditions with higher conflict.

2. Materials and methods

2.1. Participants

One hundred thirty one healthy volunteers aged from 65 to 88 ($M=70.5$, $SD=4.5$) participated in the study. 81 (61.8%) of them were female. Six participants of the Val/Val and five participants of the Val/Met group were left handed or ambidextrous. They had normal or corrected-to-normal vision. All participants received payment for their participation. The sample consisted of 79 subjects carrying the Val/Val genotype, 47 carrying the Val/Met genotype and five subjects carrying the Met/Met genotype group. The distribution of genotypes in the sample did not differ from Hardy-Weinberg equilibrium ($p=.537$), as determined using the program Finetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM). As to the expected low frequency of the Met/Met genotype, the Val/Met and Met/Met genotype were combined to one group (i.e., Val/Met–Met/Met genotype; Met-allele group). 58 participants of the Val/Val genotype (age $M=70.8$, $SD=4.7$; $MMSE=28.3$), were female (73.4%), and 23 of the combined Val/Met and Met/Met genotype group (age $M=70.2$, $SD=4.3$; $MMSE=28.7$), were female (44.2%, $X^2=11.3$, $p<.001$). The Chi-square test indicates that the factors genotype and gender are not independent in this sample. All participants were explained the scope of the study and gave written informed consent before any study protocol was commenced.

2.2. Neuropsychological testing

The participants underwent extensive neuropsychological assessment to document the neuropsychological and psychiatric status. The neuropsychological tests and the questionnaires were administered in an extra session, one day before the ERPs test was conducted. The presented data are a part of training study with a pre and a post measure (only the pre measure is reported here). However, one test (TMT) and two questionnaires (NEO-FFI and CFQ, see below) were administered during the post measure after 12 participants (five of the Val/Val and seven of the Val/Met–Met/Met genotype) dropped out from the study.

The battery comprised a number of tests and questionnaires, assessing the general cognitive status (Mini Mental State Examination (MMSE); Folstein, Folstein, & Mc Hugh, 1975), depressive disorder (Becks depression inventory; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the personality traits by NEO-FFI (“Big Five” personality factors questionnaire; Costa & McCrae, 1992). The neuropsychological tests measured attentional endurance (d2; Brickenkamp, 1994), speed of processing and vigilance (Digit-symbol-test), short-term and working memory functions (Digit-span-test), both being subtests of the Wechsler adult intelligence scale (Wechsler, 1955). Interference was assessed by the classic Stroop colour-word test (Stroop, 1935), the verbal memory was assessed by the Verbal Learning and Memory Test (VLMT; Helmstaedter & Durwen, 1990). Divergent thinking was measured by the German version of the word-fluency-test (WFT; Aschenbrenner, Tucha, & Lange, 2001) and the crystalline intelligence was examined by the multiple choice word test (MWT-B; Lehrl, 1995). Visuospatial memory was assessed by the Rey–Osterrieth complex figure test (ROCF; Osterrieth, 1944), mental rotation by the mirrored figures, a subtest from the wilde test of intelligence (Jäger & Althoff, 1994). Finally, the trail making test (TMT; Reitan, 1992) was administered to measure the psychomotor speed a task switching. The self-reported failures in perception, memory, and motor function were analyzed using the cognitive failures questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982).

2.3. Genotyping

Isolation of genomic DNA of leucocytes was performed according to standard procedures (Lehmann, Selinski, & Blaszkewicz, 2010). Analysis of the [A/G] substitution (rs6265) of BDNF on chromosome 11p14 and differentiation between the homozygous (A/A), homozygous (G/G) and the heterozygous (A/G) form of the sequence: CATCATTGGCTGACACTTTCGAACAC[A/G]TGATAGAAGAGCTGTTGGATGAGGA was detected via TaqMan Assay (e.g., Golka et al., 2009). Briefly, 5–8 ml of venous blood was taken into a 9 ml tube (Sarstedt, Nümbrecht, Germany) from the cubital vein with EDTA as the anticoagulant and was frozen at −20 °C. DNA was isolated using a QIAamp DNA blood maxi kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol (Arand et al., 1996). DNA concentrations were determined using a NanoDrop ND-1000 UV/Vis-spectrophotometer (PEQLAB Biotechnologie GMBH, Erlangen, Germany). Genotyping was performed on an ABI7500 Sequence Detection System with the use of TaqMan® assays (Applied Biosystems, Darmstadt, Germany). A final reaction volume of 15 µl was used per well of a 96-well plate. The reaction mix for amplification was prepared by mixing 7.5 µl TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA 94404, U.S.A.) and 0.75 µl Working Stock of SNP Genotyping Assay (Applied Biosystems, Foster City, CA 94404, U.S.A.) per sample. To this reaction mixture 1 µl DNA solution (with a total of 10 ng DNA) and 5.75 µl distilled water were added to achieve a final volume of 15 µl. Amplification was performed using a protocol with 40 cycles, 15 s at 92 °C (denature), 1 min at 60 °C (anneal/extend). An initial hold