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COGNITIVE NEUROSCIENCE

The brain-derived neurotrophic factor Val66Met polymorphism affects encoding of object locations during active navigation

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Abstract

The brain-derived neurotrophic factor (BDNF) was shown to be involved in spatial memory and spatial strategy preference. A naturally occurring single nucleotide polymorphism of the BDNF gene (Val66Met) affects activity-dependent secretion of BDNF. The current event-related fMRI study on preselected groups of 'Met' carriers and homozygotes of the 'Val' allele investigated the role of this polymorphism on encoding and retrieval in a virtual navigation task in 37 healthy volunteers. In each trial, participants navigated toward a target object. During encoding, three positional cues (columns) with directional cues (shadows) were available. During retrieval, the invisible target had to be replaced while either two objects without shadows (objects trial) or one object with a shadow (shadow trial) were available. The experiment consisted of blocks, informing participants of which trial type would be most likely to occur during retrieval. We observed no differences between genetic groups in task performance or time to complete the navigation tasks. The imaging results show that Met carriers compared to Val homozygotes activate the left hippocampus more during successful object location memory encoding. The observed effects were independent of non-significant performance differences or volumetric differences in the hippocampus. These results indicate that variations of the BDNF gene affect memory encoding during spatial navigation, suggesting that lower levels of BDNF in the hippocampus results in less efficient spatial memory processing.

Introduction

To successfully navigate through our spatial environment requires the interplay of multiple complex components, such as memory of locations, orientation, route planning and the integration of different types of spatial cues.

An important factor influencing an individual's spatial navigation and spatial memory abilities is genetic variations. Here, we investigated the role of a naturally occurring single nucleotide polymorphism on encoding and retrieval in a virtual navigation task. The brain-derived neurotrophic factor (BDNF) is involved in learning and memory, such as hippocampus-dependent short- and long-term

memory (Bekinschtein *et al.*, 2008a; Dincheva *et al.*, 2012), by regulating synaptic plasticity (Bekinschtein *et al.*, 2008b; Lu *et al.*, 2008). In spatial memory tasks in rodents, BDNF mRNA was increased in the hippocampus after learning in spatial mazes (Kesslak *et al.*, 1998; Mizuno *et al.*, 2000) and after spatial context learning (Hall *et al.*, 2000). Inhibiting BDNF expression in the hippocampus leads to impairments in encoding and recall of both long-term spatial memory and spatial working memory (Mizuno *et al.*, 2000). A common polymorphism in the human BDNF gene (Val66Met; rs6265) is associated with reduced intracellular trafficking and reduced activity-dependent secretion of the BDNF protein (Egan *et al.*, 2003; Chen *et al.*, 2004). In a spatial maze task in humans, it was shown that the amount of Met alleles someone carries, associated with less activity-dependent BDNF secretion in the hippocampus, correlates positively with the choice for a response

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strategy (striatum-dependent) and negatively with the choice of a hippocampus-dependent spatial strategy (Banner *et al.*, 2011). Using fMRI, the authors showed that Val homozygotes activate the hippocampus more during the first encoding trial of the maze, whereas Met carriers activate the striatum more during late learning and test phases. This might be the basis for either hippocampus-dependent or caudate nucleus-dependent spatial strategy preferences. In contrast to studies that suggest increased hippocampal involvement in Val homozygotes during memory encoding, recent studies that matched Val66Met group performance have observed increased activation for Met carriers, and encoding activations predicting retrieval success in Met carriers (van Wingen *et al.*, 2010; Dennis *et al.*, 2011), suggesting compensatory recruitment.

In this study, we used a virtual spatial navigation working memory task in event-related functional magnetic resonance imaging (fMRI) to test the hypothesis that the BDNF Val66Met polymorphism influences spatial location encoding and retrieval. During encoding, subjects learned the location of a target stimulus relative to three distinguishable columnar objects, providing positional information. An invisible sun cast shadows from these objects, providing subjects with directional information. During retrieval, minimal information to reorient was provided: either two positional cues or one positional cue with directional information was available. Expectations of which cues would be available during retrieval were manipulated in experimental blocks, which allowed us to identify the brain areas involved in encoding based on which spatial cues participants expected during retrieval. The influence of genetic variations of the BDNF Val66Met gene on this process was investigated by comparing preselected groups of Met carriers and Val homozygotes of this gene.

Materials and methods

Participants

Thirty-seven healthy right-handed adults of self-reported Caucasian ancestry participated in this study (22 males, mean age = 23.78, range 19–35). This sample is part of a larger study that was aimed at investigating how the representations of discrete object locations and configurations of objects are supported by the hippocampal and striatal systems, independent of genetic contributions. These findings are published in Wegman *et al.* (2014). To match the number of participants in each genotype group, 19 Met carriers (three homozygous, of which two men, and 16 heterozygous, of which 10 men) and 18 Val homozygotes (of which 10 men) were preselected based on Val66Met genotype with a double-blind design, and were all right-handed participants with (corrected to) normal vision and no known history of neurological or psychiatric illness. Participants were recruited from the Brain Imaging Genetics (BIG) study at the Donders Institute for Brain, Cognition and Behaviour of the Radboud University Nijmegen Medical Center, the Netherlands. This database contains genetic and imaging data of healthy adult subjects (Franke *et al.*, 2010). There were no significant differences in sex or age between the two groups ($F_s < 1$). Participants received a monetary reward or course credits for their participation, and all gave informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands) prior to participating.

Genotyping

Genetic analyses were carried out at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre, in a

laboratory which has a quality certification according to CCKL criteria. High molecular weight DNA was isolated from saliva using Oragene containers (DNA Genotek, Ottawa, ON, Canada) according to the protocol supplied by the manufacturer. The BDNF 198-GNA (rs6265) polymorphism (Val66Met) was genotyped using Taqman[®] analysis (assay ID: Taqman assay: C_11592758_10; reporter 1: VIC-C-allele, reverse assay; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). Genotyping was carried out in a volume of 10 μ L containing 10 ng of genomic DNA, 5 μ L of Taqman Mastermix (2 \times ; Applied Biosystems), 0.375 μ L of the Taqman assay and 3.625 μ L of H₂O. Genotyping was performed on a 7500 Fast Real-Time PCR System and genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). The genotyping assay had been validated before use and 5% duplicates and blanks were taken along as quality controls during genotyping.

Navigation task

Participants performed a navigation task in an open-field virtual environment (VE) inspired by the VE in Baumann *et al.*, (2010), where the expectation of availability of spatial cues during retrieval was manipulated during spatial encoding. The task is an adaptation of a task used by Baumann *et al.* (2010), showing hippocampal involvement during successful encoding and retrieval in an open-field environment with only objects available as spatial cues. By introducing uncertainty about the spatial information necessary to perform well during retrieval, this task allowed us to investigate how (well) the brain deals with unexpected spatial cues during retrieval. Furthermore, performance and brain activity in hippocampus and caudate nucleus during unexpected retrieval trials provides a sensitive test for encoding bandwidth in both genetic groups, which have been shown to differ in their hippocampus-dependent or caudate nucleus-dependent spatial strategy preferences (Banner *et al.*, 2011). The navigation task was created and administered in the Blender open source 3D package (The Blender Foundation Amsterdam, The Netherlands; www.blender.org). Participants moved through the environment by means of four buttons using their right hand mapped from their index finger to their little finger: rotate left, move forward, rotate right, move backward, respectively. Each trial consisted of an encoding and retrieval phase in which participants had to navigate toward a target that was visible during encoding but hidden in retrieval (Fig. 1). In the encoding phase of the trial, participants entered an environment that contained three colored columns and a target (a yellow pyramid). An implicit sun (not visible in the environment) cast a shadow off each column. The participants were instructed to navigate toward the target within a limited amount of time (10 s) and remember its location in the environment. Between encoding and retrieval, a blank screen was presented for 4-s. In the retrieval phase, participants re-entered the environment from one of four possible locations: the same starting location as in the encoding phase or a different location (shifted by 90°, 180° or 270° with equal probability). The target was absent and participants were instructed to navigate to where they thought the target was during the encoding phase. They confirmed its location with a button press with the index finger of their left hand. The retrieval phase had a time limit of 10 s. During the retrieval phase, objects that were present were in their original locations, but information that was previously available during the encoding phase was now missing. In objects trials, two of the previous three columns were available, but the directional information provided by the shadows was missing. In shadow trials, only one of the previous three columns were

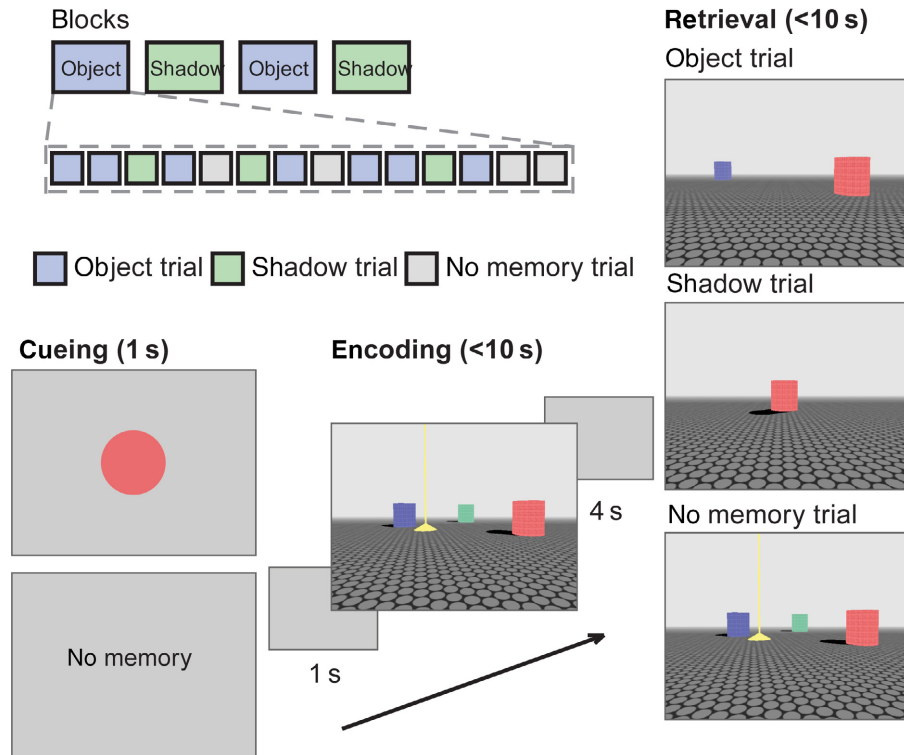


FIG. 1. Experimental paradigm. During encoding, three object cues (columns in red, green and blue) and shadows were available. Participants were required to navigate to the target object, shown in yellow. Before each trial, participants received a color cue indicating which of the colored columns would be available during retrieval. During the retrieval part of the trial, either two objects without shadows (objects trial) or one object with a shadow (shadow trial) were available. Participants were instructed to move to the position of the now unavailable target was placed and confirm with a button press. In baseline trials, indicated at the cue phase, the target was also visible during retrieval. The experiment consisted of blocks, informing participants of which type of trial would be most likely to occur (70% congruent trials, 30% incongruent trials). Note that in retrieval phases of no memory trials, the spatial cues actually visible to the participants matched the block type to strengthen the perception of the validity of the block types, i.e. in objects trials, two columns without shadows were available, and in shadow trials, one column with a shadow was available. [Colour figure can be viewed at wileyonlinelibrary.com].

available, with directional information provided by a shadow. Note that, in both trial types, the minimal information (i.e. two spatial cues) was provided to reorient within the environment. In each trial, the location of the target and the columns were different to ensure that a unique spatial layout was encoded for every trial. There was an average delay of 5 s between trials, jittered between 4 and 6 s in steps of 0.5 s.

To investigate what the effect of expected spatial information was on encoding processes in the brain, the experiment was divided into blocks, informing participants about the type of spatial cues that were most likely to be available during the retrieval phase of trials. At the start of each block, participants were informed about the upcoming block type, stating either 'objects block' or 'shadow block', which remained on the screen until participants pressed a button to continue. Within each block, 70% of the 10 experimental trials were expected (in accordance with the block type); the other three trials were unexpected, meaning that the unexpected spatial information was available during retrieval. Additionally, each block contained four 'no memory' baseline trials, in which the target was still visible during the retrieval phase. The visually available spatial cues during retrieval in these trials matched the block type to strengthen the perception of the validity of the block types, i.e. in objects trials, two columns without shadows were available, and in shadow trials, one column with a shadow was available. In addition to the block cues, at the start of each trial, participants were informed with a color cue about which of the columns available during encoding would also be available during retrieval. This cue

was presented for 1 s, followed by a blank screen for 1 s, after which the encoding phase started. In objects trials, this cue informed about the identity of one of the two columns available during retrieval. In shadow trials, this cue informed about the single column with directional information that would later be available during retrieval. This was done to make the two trial types more equal in difficulty. Without these cues, in shadow trials, participants would have to remember directional information on top of all column locations. This would render the memory requirements in objects trials a subset of those in shadow trials, thereby hampering the ability to distinguish between encoding processes for trial types in the brain. In baseline trials, the words 'no memory' were presented instead of the cue at the beginning of the trial, informing participants that the target would be available during retrieval.

Before the sessions in the scanner, participants received training in the task. Next, participants performed four training blocks inside a dummy MR scanner. Four training blocks were administered, alternating between objects and shadow blocks. This alternation was continued in the scanner sessions, with the first block type counter-balanced over subjects. The instructions combined with the training session lasted approximately 40 min. The scanning session was divided into two runs, each of which contained five blocks. This added up to 35 expected objects trials, 35 expected shadow trials, 15 unexpected objects trials, 15 unexpected shadow trials, 20 baseline objects trials and 20 baseline shadow trials. In each trial, we recorded the absolute metric error (the distance in virtual meters between the target location and the response location indicated by

the participant) as performance measure. Furthermore, we recorded duration (time in seconds it took participants to finish an encoding or retrieval phase), speed of movement (defined as the average traversed virtual meters per second), the signed rotation (the cumulative sum of angular rotations, with left rotations having a negative sign and right rotations a positive sign) and unsigned rotation (cumulative sum of angular rotations in both directions, representing the total amount of rotation).

Imaging parameters

The data were acquired on a Siemens 3 Tesla MAGNETOM Trio MRI scanner (Siemens Medical system, Erlangen, Germany) using a 32-channel coil. A multi-echo echo-planar imaging (EPI) sequence was used to acquire 31 axial slices per functional volume (voxel size = $3 \times 3 \times 3$ mm; repetition time (TR) = 2390 ms; TE = 9.4, 21.2, 33, 45, and 57 ms; flip angle = 90; field of view = 212 mm). This type of parallel acquisition sequence for functional images reduces motion and susceptibility artifacts (Poser *et al.*, 2006). After the acquisition of functional images, a high-resolution anatomical scan was acquired (T1-weighted MPRAGE, voxel size = $1 \times 1 \times 1$ mm, TR = 2300 ms, TE = 3.03 ms, 192 sagittal slices, 1 mm thick, FoV = 256 mm), accelerated with GRAPPA parallel imaging (Griswold *et al.*, 2002).

Statistical analysis

We analyzed average metric error, average time to complete encoding phases and average time to complete retrieval phases as behavioral measures within $2 \times 2 \times 2 \times 2$ ANOVAS. For average metric error and average time to complete retrieval phases, this model contained the between-subject factors genotype and sex and two within-subject factors: cues available at retrieval (objects vs. shadow) and expectancy (expected vs. unexpected). For average time to complete the encoding phase of trials, the within-subject factors in the model were block type (objects vs. shadow) and expectancy (expected vs. unexpected).

The fMRI data were preprocessed and analyzed with SPM8 (www.fil.ion.ucl.ac.uk/spm). The first four images of each session were discarded to allow for T_1 equilibration. Then, the five echoes of the remaining images were realigned to correct for motion artifacts (estimation of the realignment parameters is done for the first echo and then copied to the other echoes). The weighting of echoes for this combination was calculated based on 26 volumes acquired before the actual experiment started and was dependent on the measure differential contrast to noise ratio (Poser *et al.*, 2006). Data were subsequently spatially normalized and transformed into Montreal Neurological Institute space (resampled at voxel size $2 \times 2 \times 2$ mm³), as defined by the SPM8 EPI.nii template. Finally, the functional scans were spatially smoothed using a 3D isotropic Gaussian smoothing kernel (FWHM = 8 mm).

Statistical analyses were performed in the context of the general linear model. For each of the experimental conditions (expected objects encoding, expected shadow encoding, expected objects retrieval, expected shadow retrieval, unexpected objects retrieval, unexpected shadow retrieval), the trials were divided into low error and high error conditions according to the absolute metric error on each trial, using a median split. The time series of these experimental conditions plus no memory encoding in objects blocks, no memory encoding in shadow blocks, no memory retrieval in objects blocks, no memory retrieval in shadow blocks was convolved with a canonical hemodynamic response function and used as a regressor

in the SPM multiple regression analysis. To account for trial-by-trial differences in movement in the VE (speed of movement, signed and unsigned rotation), we modeled these effects over all trials in a run. To this end, a model was created per run for each subject, collapsing all encoding and retrieval trials into a single condition. For each trial in this model, the average speed, signed and unsigned rotation were modeled as parametric modulators. These were convolved with the hemodynamic response function (HRF) and the resulting three regressors were included in the first-level statistical models per run. Events were time-locked to when the subjects first entered the environment in the encoding and retrieval phase of each trial and were modeled for the entire period in that phase. Block cues, trial cues and missed trials were also modeled. In addition, six realignment parameters were entered as effects of no interest. Statistical analysis included high-pass filtering (cutoff, 128 s) to remove low-frequency confounds such as scanner drifts and correction for serial correlations using an autoregressive AR(1) model.

To compare the brain activity during encoding when expecting to have to rely on positional cues (in objects blocks) with that when expecting a single positional and a directional cue (in shadow blocks), we created linear contrasts of encoding phases in objects blocks minus encoding phases in shadow blocks, collapsed over expected and unexpected trials and over low and high error conditions. The resulting contrast images were entered into an independent sample *t*-test on the second level to compare general activation for this condition and to compare between genotype groups. To compare the brain activity during retrieval, the activity during experimental retrieval conditions (expected and unexpected objects and shadow trials) was compared against the corresponding baseline condition on the first level to take visual differences between the conditions into account. Note that this paper focuses on the genotype differences, for the main within-subject comparisons we refer the interested reader to Wegman *et al.* (2014).

To assess the brain regions that correlated with performance on a trial-by-trial basis, we split each of our experimental conditions (expected objects, unexpected objects, expected shadow, unexpected shadow) into a low and high error condition based on the absolute metric error using a median split. These regressors were created separately for the encoding and retrieval phases of each condition, similar to previous studies (Wolbers *et al.*, 2007; Baumann *et al.*, 2010). These effects were tested by entering the first-level linear contrast estimates in second-level random-effects analyses. For testing effects over the whole participant group, we used a one-sample *t*-test and for testing the planned contrasts of BDNF genotype, we used two-sample *t*-tests, dividing the participants in two groups (Met carriers and Val homozygotes). We tested genotype differences between encoding trials in objects and shadow blocks regardless of memory performance by taking the first-level contrasts of each experimental condition vs. its corresponding baseline and entering these linear contrast images in two-sample *t*-tests to test for genotype group differences.

Statistical inference ($P < 0.05$) was performed at the cluster level, correcting for multiple comparisons over the search volume (the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at $P < 0.001$, uncorrected.

Based on the hypothesis that BDNF affects the hippocampus and caudate nucleus during spatial memory tasks (Banner *et al.*, 2011), we used these as regions of interest (ROIs) in our functional imaging analysis. We selected these anatomically defined ROIs based on the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer *et al.*, 2002), which is based on the anatomical parcellation of spatially normalized high-resolution T1 scans in MNI space. Using

MarsBar (Brett *et al.*, 2002), we extracted average beta parameter estimate values for all voxels in each ROI for each individual first-level design. These values were entered in separate repeated-measures GLMs for encoding and retrieval phases to investigate main and interaction effects. For the encoding models, the within-subject factors block type (expected objects or expected shadow) and subsequent error (low or high) and the between-subject factor genotype (Val homozygote or Met carrier) were entered. For the retrieval phase, the within-subject factors cue available (objects or shadow), congruence (expected or unexpected) and error (low or high) and the between-subject factor genotype (Val homozygote or Met carrier) were entered, each corrected for the corresponding cue type baseline condition.

Previous studies have found volumetric differences in hippocampus related to BDNF Val66Met genotype (Pezawas *et al.*, 2004; Szeszko *et al.*, 2005; Bueller *et al.*, 2006). To exclude anatomical differences between groups as confounds in our functional analysis, we compared the volumes of left and right hippocampus and caudate nucleus between Val homozygotes and Met carriers. The automatic segmentation of the hippocampus and the caudate nucleus in our T1 images was performed using FIRST v1.2 (available at: www.fmrib.ox.ac.uk/fsl/first/index.html) in FSL 4.1.4 (available at: www.fmrib.ox.ac.uk/fsl; Smith *et al.*, 2004). This method is based on Bayesian statistical models of shape and appearance for 15 sub-cortical structures from 336 manually labeled T1-weighted MR images. To fit the models, the probability of the shape given the observed intensities is used (Patenaude *et al.*, 2011). The segmented caudate and hippocampal regions were visually inspected and overlaid on the anatomical image using FSL's 'slicedit' function to check for obvious segmentation errors (such as large parts of a structure located in the ventricles). No scans had to be removed because of this.

The volumes of the segmentations for both the left and right caudate nucleus and hippocampus were analyzed in separate independent samples *t*-tests, which were performed in SPSS 19.0 (SPSS Inc., Chicago, IL, USA). To correct the regional volumes for total brain volume, we segmented each person's anatomical image into gray matter, white matter and cerebrospinal fluid using SPM8's Unified Segmentation tool. The relative volumes of our ROIs were calculated by dividing the regional volume by the total brain volume (defined as the sum of gray and white matter) and these values were entered into the analyses.

Results

Behavioral results

We analyzed the behavioral data with $2 \times 2 \times 2 \times 2$ ANOVAs (see Methods). The results for our performance measure, average metric error, are presented in Table 1A. The average metric error was higher for females than for males ($F_{1,33} = 14.83$, $P = 0.001$). We also observed a main effect of expectancy ($F_{1,33} = 4.75$, $P = 0.037$), showing that participants performed worse on unexpected trials. We observed an interaction effect between the cue available during retrieval and expectancy ($F_{1,33} = 12.63$, $P = 0.001$). This interaction reflects a significantly higher error for unexpected shadow trials than for expected shadow trials ($t_{36} = 3.39$, $P = 0.002$), whereas the difference between unexpected objects trials and expected objects trials was not significant ($t_{36} = 0.29$, $P = 0.776$). We also observed a trend for the expectancy by sex interaction ($F_{1,33} = 3.71$, $P = 0.063$). This interaction reflects a higher error for unexpected trials than expected trials in

TABLE 1. Behavioral performance for BDNF sorted for male (M) and female (F) Val homozygotes and Met carriers. (A) Average absolute Euclidean distance error per condition. (B) Average time to complete encoding parts of trials. (C) Average time to complete retrieval parts of trials

	Met carriers		Val homozygotes	
	M	F	M	F
A				
Objects trials				
Congruent	20.07 (1.51)	28.43 (1.83)	20.13 (1.70)	28.13 (3.59)
Incongruent	21.32 (1.41)	26.38 (1.59)	20.68 (1.48)	26.53 (4.04)
Shadow trials				
Congruent	17.94 (1.28)	26.60 (2.31)	20.23 (1.75)	28.29 (4.80)
Incongruent	26.11 (1.77)	27.04 (2.11)	26.72 (1.44)	32.50 (2.87)
B				
Objects trials				
Congruent	5.83 (0.37)	5.09 (0.38)	5.72 (0.24)	4.79 (0.35)
Incongruent	5.60 (0.39)	4.98 (0.41)	5.48 (0.28)	4.80 (0.32)
Shadow trials				
Congruent	5.32 (0.32)	4.91 (0.36)	5.47 (0.26)	4.77 (0.28)
Incongruent	5.92 (0.34)	5.14 (0.42)	5.82 (0.27)	4.91 (0.40)
C				
Objects trials				
Congruent	6.55 (0.19)	6.11 (0.48)	5.89 (0.29)	5.99 (0.31)
Incongruent	6.75 (0.30)	6.39 (0.48)	6.41 (0.26)	6.32 (0.27)
Shadow trials				
Congruent	5.83 (0.20)	6.16 (0.52)	5.41 (0.27)	5.85 (0.25)
Incongruent	5.83 (0.28)	5.63 (0.56)	5.64 (0.29)	5.58 (0.29)

males ($t_{21} = 3.67$, $P = 0.001$), but no difference for females ($t_{14} = 0.11$, $P = 0.92$). We also observed a trend for the cue by genotype interaction ($F_{1,33} = 3.65$, $P = 0.065$). This interaction reflects a higher error for shadow trials than objects trials in Val homozygotes ($t_{18} = 3.18$, $P = 0.005$), but no difference in Met carriers ($t_{17} = 0.50$, $P = 0.62$). Importantly, we did not observe a main effect for genotype ($F_{1,33} = 0.50$, $P = 0.49$), nor any other interaction with genotype (all P -values > 0.40). No other main effects or interactions reached significance (all P -values > 0.40).

When analyzing the time it took participants to complete the encoding phases of trials, we observed a main effect of block type ($F_{1,33} = 7.32$, $P = 0.011$; Table 1B), showing that encoding phases in shadow blocks were completed faster than encoding phases in objects blocks. We also observed a main effect of sex ($F_{1,33} = 4.95$, $P = 0.03$), where females were faster than males. For genotype, the main effect did not reach significance ($F_{1,33} = 0.156$, $P = 0.70$), neither did any of the interactions (all P -values > 0.20).

The analysis of the times to finish the retrieval phases of trials revealed a main effect of the available cue during retrieval ($F_{1,33} = 44.40$, $P < 0.001$; Table 1C), showing that retrieval phases in shadow trials were finished faster than those in objects trials. The interaction between the available cue and expectancy was also significant ($F_{1,33} = 15.28$, $P < 0.001$), reflecting significantly longer completion times for unexpected objects trials than for expected objects trials ($t_{36} = 3.50$, $P < 0.01$), whereas the difference between unexpected shadow trials and expected shadow trials was not significant ($t_{36} = 0.828$, $P = 0.41$). The main effect of genotype did not reach significance ($F_{1,33} = 0.76$, $P = 0.39$), nor did any of the interactions including genotype (all P -values > 0.20). No other main effects, including a main effect of cue, or interactions were observed.

To ensure that the genotype groups did not differ in terms of their navigational behavior, we compared the average speed, signed rotation, and unsigned rotation within trials of each condition (encoding

and retrieval phases of expected objects, unexpected objects, no memory in objects blocks, expected shadow, unexpected shadow, no memory in shadow blocks) using independent samples *T*-tests. Furthermore, it could be that the groups used a different strategy with respect to the egocentric use of the cued column, e.g. by moving closer to it during encoding. To test this, we also compared the closest distance that subjects moved near the cued column, averaged over all trials and tested for all conditions. None of the described comparisons revealed a significant difference between the genotype groups (all *P*s > 0.09).

Structural analysis results

Using the anatomical scans, we tested whether structural differences in hippocampal and caudate volume (as percentages of total brain volume) between the BDNF genotype groups could account for the functional differences observed between these groups. There were no differences in caudate volume between the groups (left: $t_{35} = -0.34$, $P > 0.70$; right: $t_{35} = 0.14$, $P > 0.80$). There was also no difference in right hippocampal volume between groups ($t_{35} = -0.78$, $P > 0.40$), but a trend in left hippocampal volume between groups ($t_{35} = 1.85$, $P = 0.07$). To account for this trend effect of genetic group on left hippocampal volume, we added left hippocampal volume (as percentage of total brain volume) as a covariate in our imaging analysis and in the analysis on the extracted beta values from the left hippocampus.

Neuroimaging results

Encoding phases in objects blocks compared to baseline trials over the entire group of participants activated a wide array of regions, including the right hippocampus (see Table 2 and Fig. 2). Encoding in shadow blocks of the entire group activated many of the same regions, including the caudate nucleus (see Table 2 and Fig. 2). We then investigated whether there were genotype differences between encoding trials in objects and shadow blocks regardless of memory performance. We found no regions showing a difference between the genotype groups.

Next, we compared activation during encoding of spatial locations that predicted subsequent performance. The contrast of expected objects encoding trials with low subsequent error compared to such

trials with high subsequent error revealed no significant clusters, as did the comparison between high subsequent error trials compared to low subsequent error trials. However, an error by genotype interaction was found in the left hippocampus and parahippocampal gyrus, where Met carriers showed a higher difference between subsequent low and high error expected objects trials than the Val homozygotes (Table 3 and Fig. 3A). Subsequent analyses showed that the Met carriers showed a higher activation for subsequent low error compared to subsequent high error in left hippocampus and parahippocampal gyrus (Table 3). No effects on the whole brain level or in our ROIs were found for subsequent high compared to low errors in Met carriers. Val homozygotes did not show any significant regions activated in either low-high error and high-low error contrasts (Table 3). No genotype differences were observed that predicted subsequent performance for the other encoding contrasts. Analyses on extracted parameter estimates of each condition revealed an interaction between genotype and subsequent error in the left hippocampus during encoding ($F_{1,32} = 8.80$, $P = 0.006$, Fig. 3B). Met carriers showed more left hippocampal activity in encoding phases that were followed by lower error retrieval phases, as compared to high error trials, whereas the left hippocampus in Val homozygotes showed the reverse pattern (independent of expectancy). No main effects or interactions were observed in the encoding model in right hippocampus, nor in left and right caudate nucleus. The other encoding contrasts yielded no main effects of genotype or interactions containing genotype.

In the analysis of the retrieval phases of trials, we first looked for genotype differences in activation during experimental retrieval phases compared to baseline. When comparing the unexpected objects trial regardless of memory performance vs. baseline, we observed higher activity in the left caudate nucleus for Val homozygotes compared to Met carriers ($P_{SVC} = 0.015$; Table 4). Subsequent analyses showed the Val homozygotes activated the left caudate nucleus stronger compared to baseline ($P_{SVC} = 0.001$), whereas the Met carriers showed a trend to deactivate the left caudate nucleus ($P_{SVC} = 0.054$). No whole-brain significant clusters were revealed for this comparison. We did not find any other significant genotype difference in our ROIs, nor in the rest of the brain for the other retrieval conditions vs. baseline (expected objects, expected shadows and unexpected shadows). Next, we looked for activity that predicted good performance during retrieval

TABLE 2. Brain regions showing significant activations during encoding

Contrast	Region	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	Peak <i>t</i> score
Encoding in objects blocks > baseline	Bilateral occipital/middle temporal/precuneus/sup parietal/inf parietal/supramarginal	18 291*	30	-70	30	11.15
	Bilateral precentral/middle frontal gyrus/superior frontal gyrus/IFG/SMA	8859*	-30	0	58	9.21
	Left orbitofrontal cortex	219*	-16	48	-14	6.2
	Left cerebellum	383*	-10	-48	-24	5.28
	Bilateral caudate nucleus	304*	-2	18	8	5.13
	R Hippocampus	13 [†]	40	-20	-18	3.9
	R Parahippocampal gyrus	30 [†]	34	-38	-12	4.41
	R Caudate	11 [†]	20	26	0	3.77
	Encoding in shadow blocks > baseline	Bilateral occipital/middle temporal/precuneus/sup parietal/inf parietal/supramarginal/precentral/IFG	22 224	30	-70	34
Bilateral precentral/middle frontal gyrus/superior frontal gyrus/IFG/SMA		6205	-38	-2	36	6.55
L Cerebellum		400	-8	-74	-24	5.73
L Caudate nucleus		40	-16	26	-2	4.76
R Caudate nucleus		40	18	26	-6	4.89

* $P < 0.05$ at the cluster level, [†] $P < 0.05$ small volume corrected.

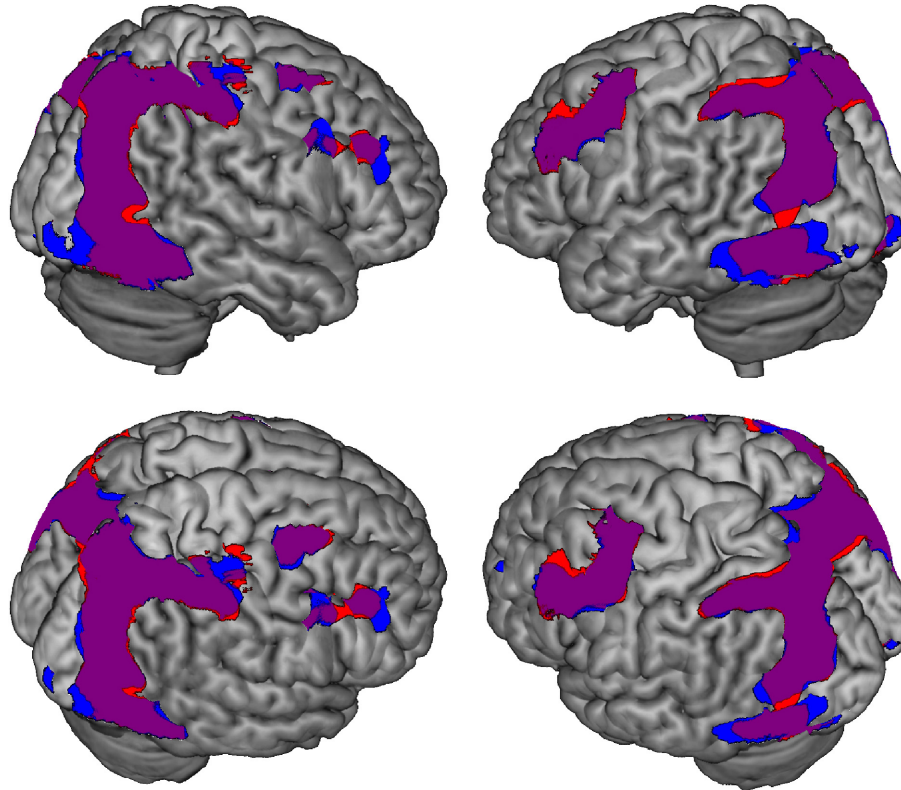


FIG. 2. Rendered three-dimensional images depicting mean BOLD activation over the entire experimental group in the whole-brain analysis during encoding. Red shading represents encoding during objects blocks compared to baseline, blue shading represents encoding during shadow blocks compared to baseline and purple shading represent overlaps. Figures display the effects at $P < 0.05$, corrected for multiple comparisons over the whole brain. [Colour figure can be viewed at wileyonlinelibrary.com].

TABLE 3. Brain regions showing a significant subsequent error (low compared to high error trials) between Met carriers compared to Val homozygotes during expected encoding trials in objects blocks

Contrast	Region	k	x	y	z	Peak t score
Expected encoding in objects blocks: low - high error: Met > Val	L Fusiform/Parahippocampal gyrus	221*	-32	-36	-18	4.84
	Bilateral Paracentral Lobule/Precuneus	212*	2	-36	72	4.57
	L Hippocampus	16 [†]	-26	-4	-26	3.96
Expected encoding in objects blocks: low - high error: Met	L Hippocampus	25 [†]	-30	-10	-20	3.84

* $P < 0.05$ at the cluster level, [†] $P < 0.05$ small volume corrected.

by comparing low error with high error trials within each condition. The difference in activity between low and high error trials did not differ between genotypes in our ROIs for any of the retrieval conditions. However, in expected shadow retrieval trials, we observed genotype differences in activity associated with successful retrieval in the right cuneus/precuneus, the cerebellum and the right superior parietal cortex (Table 5). Subsequent analyses within these regions showed that the Met carriers showed significantly higher activation for low error compared to high errors, whereas the Val homozygotes showed this effect in none of the regions. However, the Val homozygotes did show a higher activation in

the cuneus/precuneus region for high compared to low error trials (Table 5). Analysis of the beta values for each of the retrieval conditions against its corresponding baseline was performed with the within-subject factors cue available, expectancy and error and the between-subject factor genotype. We observed no significant main effects or interactions in any of our ROIs (all P -values > 0.06). The other retrieval contrasts yielded no main effects of genotype or interactions containing genotype.

Although we did not see any main effects or interactions with genotype in our memory performance measure, we also ran our second-level main models with task performance added as a covariate of no interest. This was done because brain activation differences between genotype groups in the absence of memory performance differences in those groups are problematic to interpret because fewer participants are required in imaging genetics studies to have sufficient statistical power to observe an effect than in behavioral genetics studies (Rasch *et al.*, 2010). By adding task performance for the conditions under investigation as a covariate to our statistical models, we corrected for non-significant memory performance differences between groups. The addition of performance as a covariate did not affect the obtained results. Additionally, adding sex as a covariate to the analysis did not qualitatively change the left hippocampal results, but rendered them marginally significant.

Discussion

In this paper, we show that the BDNF Val66Met genotype is relevant for the encoding of spatial object locations. Comparing preselected groups of Met carriers and Val homozygotes, the brain response during encoding between subsequent low error trials

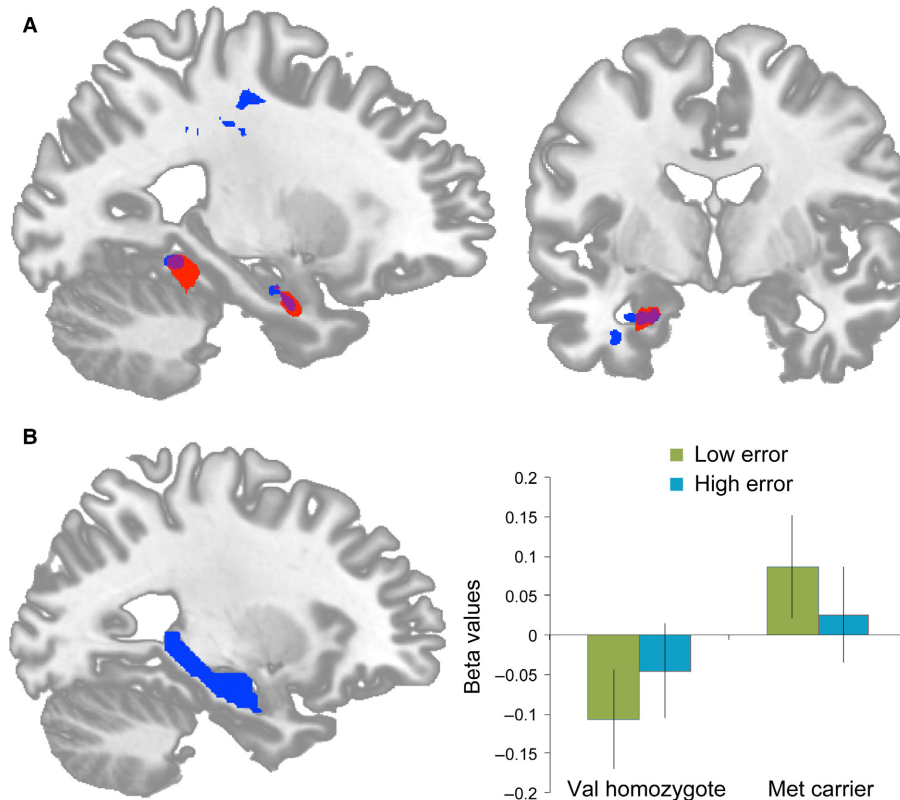


FIG. 3. The BDNF Val66Met polymorphism affects successful memory encoding in the left hippocampus. (A) Results for whole brain analysis. Red shading indicates low minus high subsequent error contrast for Met carriers higher than for Val homozygotes in the expected encoding condition. Blue shading indicates subsequent low minus high error in the Met carrier group. Sagittal section at $x = -26$, coronal section at $y = -4$. Figures display the effects at $P < 0.001$, uncorrected. (B) Results for left hippocampus ROI plot shows results for low and high error trials (collapsed over objects and shadow trial encoding conditions), separately for Val homozygotes and Met carriers. Bars represent means (\pm SEM). [Colour figure can be viewed at wileyonlinelibrary.com].

TABLE 4. Brain regions showing significant genotype effect during retrieval for incongruent objects trials

Contrast	Region	k	x	y	z	Peak t score
Retrieval for incongruent objects trials (baseline corrected): Val - Met	L Caudate	44 [†]	-16	-2	24	4.79
Retrieval for incongruent objects trials (baseline corrected): Val homozygotes	L Caudate	164 [†]	-18	-4	22	7.84
Retrieval for incongruent objects trials (baseline corrected): Met homozygotes	L Caudate	8 [‡]	-2	16	0	-4.26

[†] $P < 0.05$ small volume corrected, [‡] $P < 0.10$ small volume corrected.

compared to subsequent high error trials was different for the Val homozygotes and Met carriers. When participants expected to have to rely on multiple object positions during subsequent retrieval, the left hippocampus showed an interaction between subsequent location memory error and genotype, where only Met carriers showed increased activation with subsequent performance in the left hippocampus. An anatomical region of interest analysis over the whole left hippocampus confirmed this effect, regardless of which information participants were expecting.

Next to its role in long-term spatial memory (O'Keefe & Nadel, 1978; Burgess *et al.*, 2002; Janzen *et al.*, 2008; Wegman & Janzen,

2011), the hippocampus is also involved in spatial working memory (WM) in both two-dimensional (van Asselen *et al.*, 2006) and three-dimensional (Baumann *et al.*, 2010) tasks. For a more in-depth discussion of the behavioral and neural comparisons not related to genotype, we refer to Wegman *et al.* (2014), of which this study is a subsample. Here, we focus on the involvement of BDNF in spatial WM, which was shown in early work by Mizuno *et al.* (2000), where infusion of antisense BDNF oligonucleotide (leading to a significant reduction of BDNF mRNA and protein levels in the hippocampus) resulted in poorer spatial WM, as well as long-term memory impairments. BDNF is involved in the modulation of synaptic transmission (Berninger & Poo, 1996; Lu *et al.*, 2008), thus having an acute effect on synaptic efficacy (Schinder & Poo, 2000). Combined with the crucial role for BDNF in short- and long-term memory (Bekinschtein *et al.*, 2008a; Lu *et al.*, 2008), BDNF therefore can affect hippocampal spatial memory processing not only on long timescales but also during working memory.

The first studies into the role of BDNF in humans showed that human carriers of the Met allele showed impaired episodic and verbal memory performance (Egan *et al.*, 2003; Hariri *et al.*, 2003; Dempster *et al.*, 2005; Schofield *et al.*, 2009) and were found to have smaller hippocampal volume (Pezawas *et al.*, 2004; Szeszko *et al.*, 2005; Bueller *et al.*, 2006; but see Stein *et al.*, 2012 who failed to replicate these findings in a very large sample). In line with these results, and seemingly in contrast to our results showing an increased neural activation during successful encoding in Met carriers, previous neuroimaging studies have found decreased hippocampal activity during memory encoding and retrieval for Met carriers

TABLE 5. Brain regions showing a significant effect of successful retrieval for Met carriers compared to Val homozygotes

Contrast	Region	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	Peak <i>t</i> score	Peak voxel	Peak voxel low-high	Cluster <i>P</i> value	Cluster <i>P</i> value	Cluster <i>P</i> value
							<i>T</i> value in Met carriers	error <i>T</i> value in Val homozygotes	Met carriers low - high error	Val homozygotes low - high error	Val homozygotes high-low error
Retrieval in congruent shadow trials: low - high error: Met > Val	R precuneus/cuneus	257*	30	-50	28	4.66	2.8	-3.85	0.009	n.s.	0.005
	Cerebellum	259*	2	-58	-16	4.66	6.44	-0.8	< 0.001	n.s.	n.s.
	R superior parietal cortex	189*	20	-68	52	4.52	5.71	-1.22	< 0.001	n.s.	n.s.

* $P < 0.05$ at the cluster level, n.s. = not significant.

(Hariri *et al.*, 2003; Hashimoto *et al.*, 2008). On the other hand, a recent study showed increased neural activity in Met carriers during a similar scene encoding and retrieval task (Dennis *et al.*, 2011). In this study, there was no memory difference between genotype groups. Decreased neural activity for Met carriers in Hariri *et al.* (2003) might therefore be confounded with worse memory performance. Dennis *et al.* (2011) additionally administered an event-related relational memory task, which allowed for the exploration of brain activity predicting successful memory encoding and retrieval. This task revealed greater medial temporal lobe activity predicting encoding and retrieval success for Met carriers compared to Val homozygotes. In line with these results, a higher subsequent memory effect (brain activity predicting whether an item will be remembered later) for male Met carriers was reported in van Wingen *et al.* (2010). Again, this occurred in the absence of memory performance differences between BDNF genotype groups. These findings can be interpreted in two distinct ways. First, these findings could be the result of neural inefficiency. The Met allele is associated with reduced activity-induced BDNF secretion (Egan *et al.*, 2003; Chen *et al.*, 2004), which might require more neural activation or a larger population of neurons to induce long-term potentiation. Indeed, an ERP study into error-related processing suggests less efficient neural network communication in Met carriers. (Beste *et al.*, 2010). This points to a compensatory mechanism in Met allele carriers, where increased neural processing in the hippocampus is required to equal memory performance compared to Val homozygotes. In circumstances where this compensatory mechanism fails, Val homozygotes would exhibit better memory performance, as observed in Hariri *et al.* (2003). Another possibility is that Met carriers encoded the environment in a qualitatively different way, e.g. leading to different or more features of the spatial environment being encoded or leading to longer lasting representations. Although we cannot address the latter possibility, a difference in the encoding of environmental features seems unlikely. If this were the case, we would expect an interaction between genotype and expectancy. We did not see this, although we did observe a trending genotype by cue interaction. Notwithstanding, including performance as a covariate in our functional imaging analyses did not change the results.

The current results show BDNF effects on encoding success. During spatial memory retrieval, we observed effects of BDNF genotype on retrieval memory success in the cuneus/precuneus, cerebellum and superior parietal cortex during expected shadow trials. The precuneus is involved in both imagining rotations of one's own viewpoint and of objects in a scene (Lambrey *et al.*, 2012). This study also found that the rotation of objects in an environment more than the rotation of the self within an environment activated

the superior parietal cortex. Moreover, the parietal cortex is involved in successful retrieval during episodic memory tasks (Cabeza *et al.*, 2008). The cerebellum seems to participate in the procedural components of navigation (Rondi-Reig & Burguière, 2005) and has been found to be activated by successful detour navigation (Maguire *et al.*, 1998). Surprisingly, during retrieval, we did not observe effects of genotype on successful retrieval in the hippocampus. Furthermore, over both groups, we did not observe hippocampal activation related to successful memory retrieval. This is in contrast with the study by Baumann *et al.* (2010), who employed a similar task and observed within-participant performance effects in hippocampus during both encoding and retrieval. Although our study uses a similar task, it differs in one important way; in our study, the type of cues and (in the case of objects trials) which specific cues would be available during retrieval were designed not to be completely reliable. Therefore, encoding and retrieval strategies that would be successful in a real-world setting might be unsuccessful in some trials on our task. These trial-by-trial differences in attended object features or employed strategies therefore introduce variability in our performance measure. More hippocampal involvement during encoding might still lead to better all-round memory performance, explaining the observed difference between trials subsequently remembered with low and high errors. New spatial configurations compared to old ones have shown hippocampal activation (Düzel *et al.*, 2003). In line with this suggestion, studies have found higher hippocampal responses to novel compared to correctly recognized stimuli (Daselaar *et al.*, 2006; Vilberg & Rugg, 2009) and indistinguishable hippocampal responses to missed compared to correctly recognized stimuli (Yu *et al.*, 2011; Rugg *et al.*, 2012), especially when successful recognition lacks in retrieval of contextual details. Although the absence of an effect during retrieval should be interpreted cautiously, it might be that the failing recollection process during retrieval of high error trials is accompanied by novelty-induced encoding of the spatial configuration, which contains only a subset of the information available during encoding.

Although Banner *et al.* (2011) found that Met carriers compared to Val homozygotes activate the caudate nucleus more strongly during late encoding and retrieval, we observed that the left caudate nucleus was activated more strongly by Val homozygotes during retrieval in unexpected objects trials, in which participants were expecting a shadow trial. This could be related to different strategy use by the genotype groups. The caudate nucleus is associated with stimulus-response learning, in which a stimulus is consistently associated with a correct response (Packard & McGaugh, 1996; Iaria *et al.*, 2003). In support of this suggestion, Val homozygotes and Met carriers have been shown to use different navigational strategies

(Banner *et al.*, 2011). However, we only observed genotype differences independent of performance in one retrieval condition, arguing against a consistent use of different strategies by the genotype groups. Also, the task used in the fMRI study by Banner *et al.* (2011) and the current one differ considerably, meaning further research investigating the role of BDNF on caudate nucleus functioning in spatial tasks is necessary.

The behavioral part of the study reported by Banner *et al.* (2011) showed that the amount of Met alleles someone carries predicts the spontaneous use of a non-spatial strategy in a virtual maze task. The use of such a non-spatial strategy predicts worse performance on a wayfinding task in a more realistic virtual town (Etchamendy & Bohbot, 2007), suggesting BDNF might affect the ability to create a cognitive map of places in an environment. The environment in our task is relatively simple and we did not observe performance differences between our genotype groups. Therefore, it could be that, in a more complex spatial environment, the less efficient hippocampal processing of Met carriers cannot be compensated by increased hippocampal activation in order to perform equally well (van Wingen *et al.*, 2010; Dennis *et al.*, 2011). Future studies should investigate the influence of the BDNF gene in more large-scale virtual and real environments.

Several factors can complicate the interpretation of genetic differences in functional imaging studies. For example, significant between-group neural activity differences might be confounded by anatomical differences related to genotype. To ensure our results in left hippocampus were not affected by the observed trend toward volumetric differences in the left hippocampus between BDNF groups, we controlled for this in our analysis. Furthermore, brain activation differences between genotype groups in the absence of memory performance differences in those groups are problematic to interpret because fewer participants are required in imaging genetics studies to have sufficient statistical power to observe an effect than in behavioral genetics studies (Rasch *et al.*, 2010). We addressed this concern by adding performance on the conditions under investigation as covariates to our analyses, which did not affect the outcomes.

In order to equalize the shadow and object trials in difficulty, we have provided the minimal two pieces of spatial information needed to reorient during retrieval. Nevertheless, participants could focus on only a single landmark during shadow encoding trials, ignoring the others and encoding the shadow as a second landmark, making differences between shadow and objects trials a reflection of the number of object locations that have to be kept in WM. Speaking against this possibility, we did not observe a statistically significant performance difference between expected and unexpected objects trials. This indicates that, when expecting a shadow retrieval trial, participants also encoded the positions of all landmarks at least to the degree to enable their use for reorientation. Furthermore, a meta-analysis on working memory studies (Rottschy *et al.*, 2012) revealed no WM load-dependent effects in the hippocampus. In a virtual environment study in which object locations had to be tracked in an egocentric manner, the hippocampus also did not exhibit increased activity with an increased number of object locations to be tracked in WM. Together, it seems unlikely that the observed effects in the hippocampus are due to WM load.

This study is, to the best of our knowledge, the first to demonstrate that the BDNF Val66Met polymorphism plays a role in the successful encoding of object locations. Diverse results have been found for BDNF in imaging studies. The results presented here are most in line with a compensation account for Met carriers. In the absence of memory performance differences, Met carriers showed

increased hippocampal activation during successful encoding. These effects could not be accounted for by subtle non-significant differences in memory performance or differences in gray matter volume between our genetic groups. These results provide valuable insights into the genetic contributions to spatial memory encoding in the human brain.

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