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A functional variant of the tryptophan hydroxylase 2 gene impacts working memory: A genetic imaging study

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Abstract

Imaging studies have demonstrated that prefrontal and parietal regions are activated during working memory (WM) tasks. Recently some molecular genetic studies reported associations between a functional promoter polymorphism of the tryptophan hydroxylase 2 gene (TPH2), that regulates the synthesis of serotonin, and attention.

In 49 healthy Caucasian subjects the role of the TPH2 −703 G/T polymorphism for WM was tested by means of an imaging genomics approach in an *n*-back task.

fMRI data showed an increased activation for the 2-back as compared to the 0-back condition for a large network in prefrontal and parietal areas. Although behavioural data showed no performance differences between the genotype groups of the −703 G/T a significantly stronger activation of the TT genotype carriers in BA 6, BA 46, and BA 40 was visible in contrast to the GT and GG groups. Present findings in congruence with previous findings support the hypothesis that TT carriers compensate deficits in executive control functions by increased brain activity.

Keywords: Working memory; Executive control; fMRI; Tryptophan hydroxylase; TPH2 gene; TPH2 −703 G/T

1. Introduction

Working memory (WM) is a central cognitive function that operates when information has to be retained and manipulated over brief periods of time (Linden, 2007). The information can be extracted from the environment or is retrieved from long-term memory. The manipulation of the information may be necessary to make it useful for goal-directed behaviour (D'Esposito, 2007). According to Baddeley's (2000) seminal multicomponent model of WM two independent slave-systems that process different types of information are distinguished, the phonological loop for verbal and the visuospatial sketchpad for visual information. The central executive integrates information from different resources by a unitary control mechanism. A fourth component, the episodic buffer provides a link between information from working memory and long-term memory.

There is agreement that the prefrontal cortex as well as the parietal cortex play a crucial role for WM. However, it is not clarified whether the WM-related activity in these regions is partly modality (visual or phonological) and stimulus specific (e.g. letters, words, shapes) (Linden, 2007), or if a process-specific approach is more suitable to account for a functional subdivision of frontal area. By means of imaging studies the neuroanatomical underpinnings of WM can be investigated. We used this approach to investigate the impact of the serotonergic system on the function of the working memory using visual stimuli such as digits.

One of the most popular paradigms used to identify the neural basis of WM is the *n*-back task of which numerous variants are available. In the most common variant of this task, the subject is required to monitor a series of stimuli and to respond whenever a stimulus is presented that is the same as the one presented *n* trials previously, where *n* is a pre-specified integer, ranging from one to four. In another variant of the *n*-back task the subject is required to respond continuously to a digit presented *n* trials previously. *n*-Back tasks allow an increase of working memory load by simply increasing the parameter *n*. With $n = 0$ a control task is constituted that requires comparable cognitive functions for task solving except the involvement of working memory functions. The *n*-back task

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in general requires monitoring, updating, and manipulation of information hold on-line.

In a comprehensive meta-analysis based on 24 fMRI studies Owen et al. (2005) identified the core brain regions involved in WM as assessed by the *n*-back task. The following cortical regions were consistently activated: lateral premotor cortex, dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal poles, and medial and lateral posterior parietal cortex. It has been demonstrated that there exist pronounced individual differences in WM performance (Jarrold and Towse, 2006) which are substantially influenced by genetic factors. Heritabilty estimates of working memory processes in a twin study of middle aged-men ranged from 0.27 to 0.51 (Kremen et al., 2007). The specific genes that constitute this heritability are mostly unknown although first candidate genes have been identified. Repeatedly, a functional gene variant in the catechol-*O*-methyltransferase (COMT) gene has been shown to be involved in prefrontal executive functions including the *n*-back task (for a review see Goldberg and Weinberger, 2004). This single nucleotide polymorphism (SNP; rs4680) is a nonsynonymous G → A base pair substitution in the coding sequence of the gene, producing a valine → methionine substitution at position 158 of the membrane-bound allozyme that predominates in the brain (MB-COMT; position 108 of the soluble allozyme S-COMT) (see review by Tunbridge et al., 2006). The 158Met form is less thermostabile than the Val158 form and thus has lower activity at physiologically relevant temperatures (Lachman et al., 1996); in brain, Met158 homozygotes have an approximately one-third diminution in activity compared to Val158 homozygotes (Chen et al., 2004). The COMT VAL158 is the best replicated gene variant shown to be associated with cognitive functions so far.

Although the focus of molecular genetic research committed to cognition was largely on genes related to the dopaminergic system, the serotonergic (5-HT) system attracts more and more attention. Inspired by pharmacological studies demonstrating the relevance of the 5-HT system for cognition (Cuccaro et al., 1993; Evers et al., 2005; Poyurovsky et al., 2003) first positive associations between polymorphisms of the 5-HT system and cognitive functions have been reported. de Quervain et al. (2003) found that a functional variant of the 5-HT2a receptor gene leading to an amino acid exchange his → tyr is related to verbal episodic memory performance. Carriers of the rare tyrosine variant showed a 21% poorer memory performance than histidine homozygous subjects. In three other studies executive control was related to a functional polymorphism in the promoter region of the tryptophan hydroxylase 2 (TPH2) gene. Tryptophan hydroxylase is the rate-limiting enzyme of 5-HT synthesis. The functionality of this promoter SNP and two other gene loci in close proximity building together a haplotype block was recently demonstrated by investigating RNA expression rates (Scheuch et al., 2007). Until now, three studies are available that have demonstrated the role of the TPH2 gene for executive functions, however the phenotypes under investigation were slightly different across studies. In a first study, the rare TT genotype of the TPH2 −703 G/T SNP (rs4570625) was related to significantly longer reaction times and significantly more errors in a conflict task of the attention network test (ANT) (Reuter et al., 2007a). The conflict task is a measure of the executive control network of attention proposed by Posner and Dehaene (1994). Functional imaging studies had shown that the executive control network was regulated by the anterior cingulate and the lateral prefrontal cortex (Fan et al., 2005). In a twin study, heritability of the executive control network could be demonstrated, whereas there was no convincing evidence for heritability of the other two networks, alerting and orienting, proposed in the attention network model (Fan et al., 2001). In a second study, testing the impact of the TPH2 −703 G/T SNP on attention by means of a continuous performance task, poorer performance was reported for carriers of the T-allele (Strobel et al., in press). However, this study could not test if this effect was based on the TT genotype as indicated in the previous study because the participants were invited to the experiment at random and not according to a testing after a priori genotyping strategy used in the Reuter et al. (2007a) study to enhance the number of the rare TT genotype carriers (prevalence 3–4% in Caucasians). A third study reporting an association between an intronic SNP on the TPH2 gene, located in close proximity to the −703 G/T SNP, and a stop-signal task, underlines the importance of the TPH2 gene for executive control processes (Stoltenberg et al., 2006).

The aim of the present study was to test if the TPH2 −703 G/T SNP was also related to WM performance, postulated to be controlled by a central executive control mechanism (Baddeley, 2000). It is assumed that executive control seems to be a basal process inherent to many cognitive functions including working memory and attention. By combining a molecular genetic with an fMRI approach we were able to test if the activity of those neural regions shown to be involved in WM (Owen et al., 2005) is modulated dependent on the genotype/alleles of the TPH2 −702 G/T SNP.

2. Methods

2.1. Participants

Forty-nine healthy Caucasian subjects (men: $n = 19$, women: $n = 30$; age: $M = 27.4$, S.D. = 6.3) participated in the study after having given informed consent. Neither the participants nor their first-degree relatives had a history of axis I psychiatric disorders. All subjects were right-handed as assessed with the *Edinburgh Handedness Inventory* (Oldfield, 1971). The study was approved by the ethical committee of the University of Giessen, School of Medicine.

2.2. Genetic analyses

DNA was extracted from blood samples. Automated purification of genomic DNA was conducted by means of the MagNA Pure® LC system using a commercial extraction kit (MagNA Pure® LC DNA isolation kit; Roche Diagnostics, Mannheim, Germany). Genotyping of the TPH2 −703 G/T polymorphism and the COMT VAL158MET polymorphism was performed by real-time PCR using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany). By means of the melting curve analyses SNPs can be detected without conducting gel electrophoresis or ensuing sequencing after amplification. The primers and hybridization probes (TIB MOLBIOL, Berlin, Germany) and the PCR protocol for the TPH2 −703 G/T are as follows:

- forward primer: 5′-TCCATATAACTCTGCATAGAGGCA-3′;
- reverse primer: 5′-GATATCCATTGCCTCAAGCA-3′;
- anchor hybridization probe: 5′-LCRed640-CATGCAAATGTGT-GAGTGTATATATGTGTAATG-phosphate-3′;
- sensor [G] hybridization probe: 5′-TCTGACTTGACATATTC-TAATTTTG -fluorescein-3′.

The PCR run comprised 55 cycles of denaturation (95 °C, 0 s, ramp rate 20 °C s^{-1}), annealing (61 °C, 10 s, ramp rate 20 °C s^{-1}), acquisition of the fluorescence signal (40 °C, 1 s, ramp rate 20 °C s^{-1}) and extension (72 °C, 10 s, ramp rate 20 °C s^{-1}) which followed an incubation period of 10 min (95 °C) to activate the FastStart Taq DNA polymerase of the reaction mix (Light Cycler FastStart DNA Master Hybridization Probes, Roche Diagnostics). After amplification a melting curve was generated by keeping the reaction time at 40 °C for 2 min and then heating slowly to 75 °C with a ramp rate of 0.2 °C s^{-1}. The fluorescence signal was plotted against temperature to yield the respective melting points (T_m) of the two alleles. T_m for the T allele was 51.6 and 58.8 °C for the G allele.

2.3. Procedures

WM performance was measured by a frequently used version of the *n*-back task (e.g. Goldberg et al., 2003). In this task a digit between one and four was displayed on a computer screen for 500 ms with an inter-stimulus interval of 1360 ms. In the 0-back control trial subjects have to respond to the present stimulus by pressing as fast as possible the corresponding response button. In the 1-back condition in which a working memory load is imposed above and beyond instructional context, the subject responds to the stimulus presented one back in sequence. Thus, the subject must continuously maintain information in working memory that was 'one back' in a sequence. In the 2-back condition, the subject must continuously respond to the stimulus that was 'two back'. Thereby, demands upon updating the content of working memory are increased. *n*-Back performance was scored as the percentage of correct responses (Goldberg and Weinberger, 2004) and reaction times. However, due to technical problems, reaction times of six participants (three GT and three GG) were not exactly recorded.

The task was presented in a block design with seven blocks of each 0-, 1- and 2-back trials alternating. Each block consisted of 11 stimuli à 0.5 s and lasted for 21 s, with 5 s of task instruction and 1 s of blank screen between the blocks. The sequence of tasks was varied randomly between subjects.

2.4. fMRI data acquisition and analysis

BOLD fMRI data acquisition was conducted by means of a 1.5 T GE Signa Scanner (General Electric, Milwaukee, WI) and a standard head coil. A T2*-weighted echo planar imaging sequence was used to acquire 28 axial slices in interleaved order aligned with the AC-PC axis (5 mm thickness, no gap, TR = 3000 ms, TE = 50 ms, field of view = 24 cm × 24 cm and flip angle = 90°). Preprocessing as well as statistical processing of the images was performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). In a first preprocessing step, images were realigned to the first volume. Thereafter, the images were spatially normalized into a standard stereotactic space (MNI template), resliced to 3 mm isotropic voxels and smoothed with a 7 mm FWHM Gaussian kernel.

In a first-level fixed-effect analysis a general linear model modeling the three *n*-back conditions was estimated. To control for movement and technical artifacts, the movement parameters as derived from the realignment step of the preprocessing as well as time series of no interest from white matter and cerebrospinal fluid (CSF) were used as covariates. The nuisance covariates were obtained by segmenting the averaged normalized T1-weighted anatomical images of all subjects and using the smoothed CSF and white matter segments to mask the individual functional time series. Then the first eigenvariates of the individual time series of the voxels within the masks were extracted. This method has been demonstrated to effectively reduce non-white noise from fMRI time series (Lund et al., 2006).

From the first-level model the contrasts 2-back > 0-back, 2-back > 1-back and 1-back > 0-back were obtained and included into a second-level random-effect analysis. Task main effects were calculated using one sample *t*-tests, group comparisons were calculated using an one-way ANOVA with the three genotypes as group factor. Activations were analyzed within regions of interest comprising all regions found to be involved in WM tasks in the meta-analysis by Owen et al. (2005). Masks were constructed using the MARINA software tool (Walter et al., 2003). For main task effects, the threshold for significance was set at $p < .05$, corrected for multiple comparisons within the entire brain using the family-wise error correction (FWE, Worsley et al., 1996). For group comparisons, a small volume correction was used reducing the number of comparisons to the number of voxels within each region of interest (ROI). Again FWE correction and a threshold of $p < .05$ were used.

3. Results

The genotype frequencies for the TPH2 −703 G/T polymorphism (TT: $n = 5$; GT: $n = 15$; GG: $n = 29$) were in Hardy–Weinberg equilibrium ($\chi^2 = 1.85$, d.f. = 1, n.s.). Although the genotype groups were not a priori balanced according to gender or age there were no significant differences between the genotype groups with respect to age ($F_{(2,46)} = 1.42$, $p = .252$) or gender ($\chi^2 = 4.32$, d.f. = 2, $p = .115$).

3.1. Working memory performance

The analysis of the percentage of correct responses revealed a significant main effect of task condition ($F_{(2,86)} = 13.41$, $p < .001$) but neither a group difference ($F_{(2,43)} = 0.09$) nor a task by group interaction ($F_{(4,86)} = 0.16$) was found. Post hoc comparisons revealed significant differences between all three task conditions but no group differences, neither for the 0-back nor for 1-back or the 2-back condition (Fig. 1). The analysis of reaction times revealed only a trend toward a significant main effect of task condition ($F_{(2,74)} = 2.76$, $p < .08$) with slightly faster responses during 2-back than during 0-back but neither a group ($F_{(2,37)} = 0.59$) nor a group by task interaction ($F_{(2,39)} = 0.97$). Again, post hoc tests revealed no significant difference between groups for any task condition. Performance did not significantly differ between male and female participants ($F_{(1,43)} = 1.05$, for accuracy and $F_{(1,37)} = 0.142$, for reaction times).

3.2. fMRI results

When comparing the activation during the 2-back condition with the activation of the 0-back condition, an increased

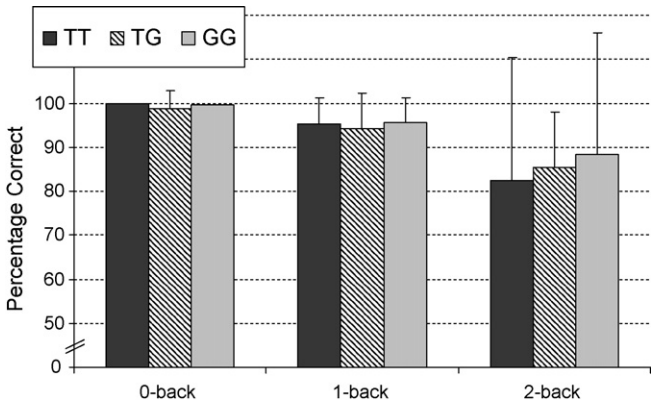

Fig. 1. Percentage of correct responses and standard errors of means for the three *n*-back condition separately displayed for the three TPH-2 genotype groups.

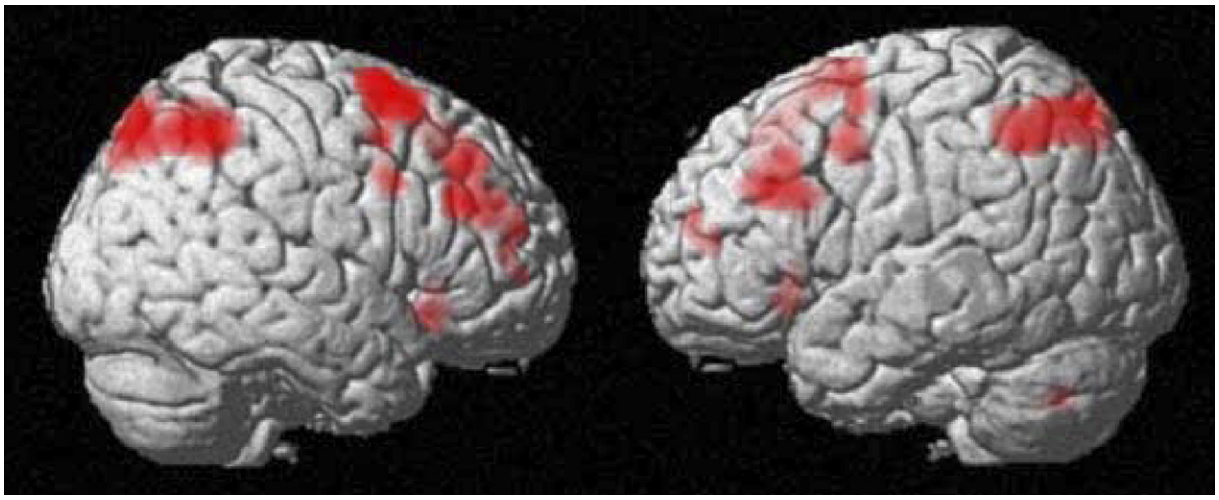

Fig. 2. Network activated during the 2-back condition compared to the 0-back condition (all subjects, see Table 1 for details on the regions activated).

activation for the 2-back condition was found for a large network including those prefrontal and parietal areas reported in the meta-analyses on *n*-back tasks by Owen et al. (2005) (see Fig. 2). Comparable activations were observed for the 1-back > 0-back contrast. Table 1 displays the significant activations derived from both analyses. Therefore, we can conclude that the *n*-back task used was suitable to investigate the neurobiological correlates of working memory.

The ANOVA comparing genotype groups revealed a stronger increase of activation from 0-back to 2-back in the TT genotype group compared to the GT and the TT groups. Stronger activation in the TT group was found for the left dorsolateral prefrontal cortex (BA 46), the bilateral premotor cortex (BA 6) and the left parietal cortex (BA 40) (see Fig. 3). For the 1-back > 0-back contrast this effect was only detectable for the left BA 6 (MNI coordinates: −33,0,66, $T = 4.89$, $p < .001$). No other WM-associated region showed a stronger activation in the TT subjects as compared to the two other genotype groups. Table 2 summarizes the ANOVA results.

No ROIs with stronger activations in subjects with at least one G allele (GG/GT) were found, neither for the 2-back nor for the 1-back condition.

4. Discussion

The present study combined a molecular genetic with a functional imaging approach to identify the neuronal and biochemical basis of working memory. Particularly the

Table 1
Most significant voxel and largest activated cluster within the WM-associated areas for the 2-back (left part) and the 1-back condition (right part). Significance levels are corrected for the entire brain volume (family-wise error correction)

Broadman area	2 back > 0 back					1 back > 0 back				
	Coordinates (MNI)	*T*	Significance (*T*)	Cluster size (*k*)	Significance (*k*)	Coordinates (MNI)	*T*	Significance (*T*)	Cluster size (*k*)	Significance (*k*)
BA 6										
L	−45,0,42	7.39	$p < .0001$	18	$p < .0001$	−45,3,39	7.97	$p < .0001$	13	$p < .0001$
R	30,12,63	12.24	$p < .0001$	90	$p < .0001$	21,9,69	8.77	$p < .0001$	58	$p < .0001$
BA 7										
L	−36,−63,48	8.74	$p < .0001$	80	$p < .0001$	−30,−72,51	7.35	$p < .0001$	45	$p < .0001$
R	30,−78,45	9.93	$p < .0001$	136	$p < .0001$	30,−78,45	9.50	$p < .0001$	44	$p < .0001$
BA 9										
L	−51,24,39	7.81	$p < .0001$	16	$p < .0001$	−45,3,39	7.97	$p < .0001$	10	$p < .0001$
R	42,36,39	8.44	$p < .0001$	38	$p < .0001$	42,39,29	5.68	$p < .01$	17	$p < .0001$
BA 10										
L	−36,57,19	6.44	$p < .005$	2	n.s.					
R	39,54,21	7.45	$p < .0001$	18	$p < .0001$	45,48,24	5.68	$p < .001$	1	n.s.
BA 40										
L	−42,−54,45	9.99	$p < .0001$	73	$p < .0001$	−39,−57,45	8.43	$p < .0001$	53	$p < .0001$
R	51,−48,51	12.55	$p < .0001$	102	$p < .0001$	48,−51,54	7.77	$p < .0001$	43	$p < .0001$
BA 46										
L	−51,21,27	6.85	$p < .0001$	6	n.s.	−54,21,27	5.46	$p < .05$	2	n.s.
R	51,39,27	8.07	$p < .0001$	26	$p < .0001$	42,36,21	5.88	$p < .01$	9	n.s.

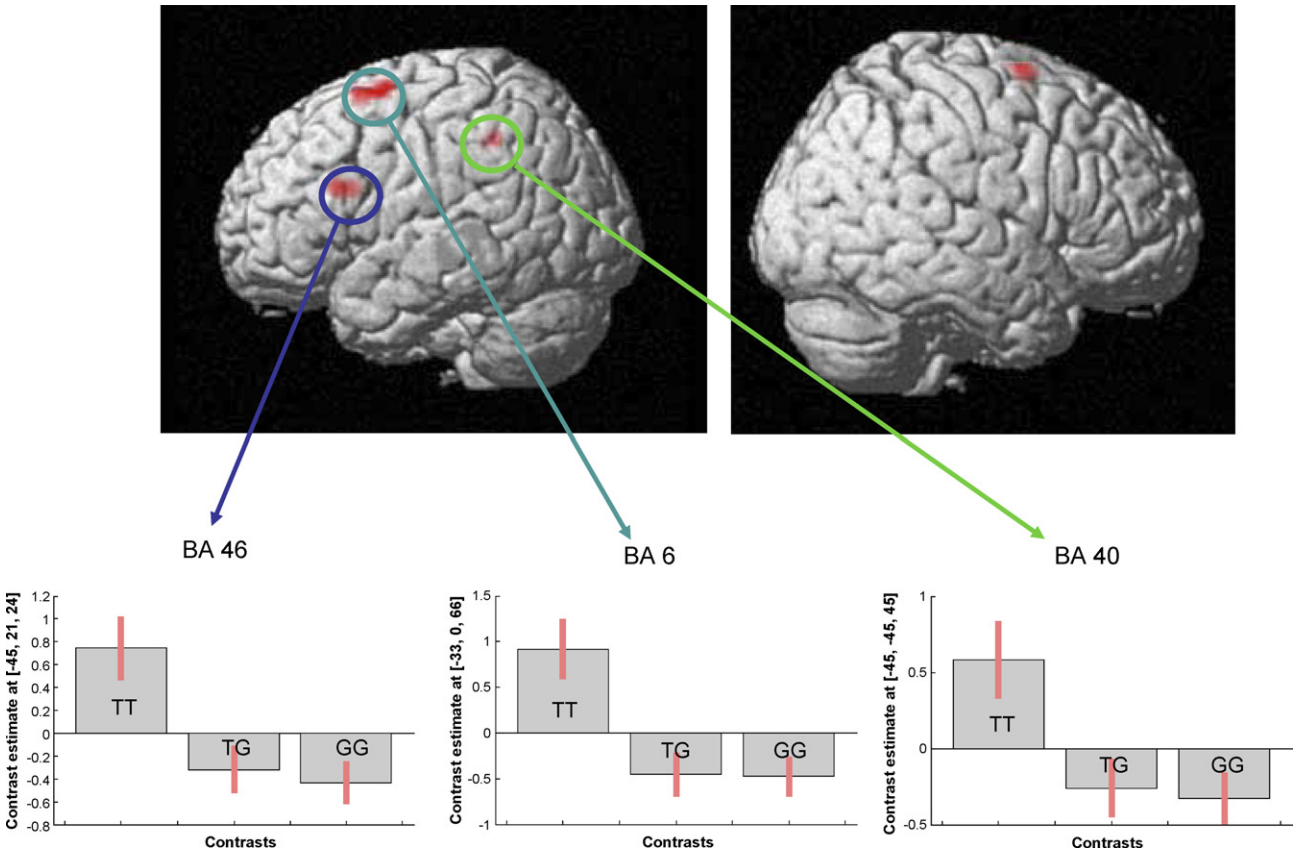

Fig. 3. Regions with increased activation in TT genotype carriers during the 2-back condition compared to the 0-back condition (upper part). The bar graphs in the lower part represent the contrast estimates ± standard error for the peak voxel within the three significant left side activations demonstrating a stronger activation exclusively for the TT group.

relevance of a functional SNP in the promoter region of the serotonergic TPH2 gene for working memory performance was tested. Previously this −703 G/T SNP has been related to different cognitive tasks (ANT, CPT, stop-signal task) all of which are implying executive control (Stoltenberg et al., 2006; Reuter et al., 2007a; Strobel et al., in press). A well established variant of the *n*-back task was applied to test if working memory – also controlled by a central executive (Baddeley, 2000) – is also related to the −703 G/T SNP.

On the behavioural level there were no differences in WM performance between genotypes or groups defined by the presence of the T or G allele. However, there was an increase in the bold response from the 0-back to the 2-back condition observable in a large network including prefrontal and parietal areas reported to be essential for WM in a recent meta-analysis (Owen et al., 2005). The −703 G/T SNP could explain individual differences in the hemodynamic responses in these regions. It turned out that in some of our regions of interest, the increase of activation from 0-back to 2-back was stronger in the TT genotype group than in the GT or the GG genotype groups (see Fig. 2). Regions with stronger activation in the TT group were the left dorsolateral prefrontal cortex (BA 46), the bilateral premotor cortex (BA 6) and the left parietal cortex (BA 40) (see Fig. 3 and Table 2). No ROIs with stronger activation in subjects with at least one G allele (GG/GT) were found. However, this difference could only be observed under high working memory load. For the 1-back condition only a marginal difference in the premotor region was observed.

When taking into account that TT subjects showed reduced cognitive performance in other studies (Reuter et al., 2007a),

Table 2
Results of the ANOVA analyses: increased activation for the 2-back (upper part) and the 1-back condition (lower part) in subjects carrying the TT genotype. Significance levels are corrected for the region of interest (family-wise error correction)

Broadman area	Coordinates (MNI)	*T*	Significance (*T*)	Cluster size (*k*)	Significance (*k*)
2 back > 0 back					
BA 6, L	−33,0,66	4.60	$p < .001$	27	n.s.
BA 40, L	−42,−48,42	3.36	$p < .032$	20	n.s.
BA 46, L	−45,18,27	3.26	$p < .027$	6	n.s.
1 back > 0 back					
BA 6, L	−33,0,66	4.89	.001	22	n.s.

the increase of activation in the working memory-associated regions must be interpreted as reflecting compensatory activation. This interpretation is supported by the fact that we could not find performance differences between genotype groups neither for the 0-back nor for the 1-back or 2-back conditions. Obviously the present findings corroborate the *effort hypothesis* stating that deficiencies in cognitive ability can be compensated by increased effort. The increased effort is reflected by stronger activation of the brain areas involved in the particular task (Larson et al., 1995).

The present study is in congruence with previous studies demonstrating impaired executive control in carriers of the TT genotype or carriers of at least one T-allele of the TPH2 −703 G/T polymorphism (Reuter et al., 2007a; Strobel et al., in press). Interestingly this finding is consistent across different types of cognitive tasks. Therefore, the effect of the TPH2 variant is not specific for attention, impulse control, or WM but seems to reflect one common basal cognitive process. We assume that this common process reflects executive control as proposed in the attention network theory by Posner and Dehaene (1994) and by the theory on WM by Baddeley (2000). Further support for this hypothesis comes from another field: personality theorists postulate that the trait of impulsivity is also related to impaired executive control. We could demonstrate that exactly the TT genotype of the TPH2 −703 G/T that was associated with a stronger BOLD response during the WM task have significantly lower harm avoidance (HA, a trait highly correlated with anxiety and neuroticism) and higher extraversion scores (Reuter et al., 2007b). This configuration of high neuroticism and high extraversion reflects impulsivity according to Gray's influential personality theory (Gray, 1973). In sum, the present and recent findings underline the importance of the TT genotype of the functional TPH2 −703 G/T polymorphism for executive control and phenotypes as attention, WM, and impulse control which are under the influence of this basal relay structure in the central nervous system. The executive control system seems to be a network consisting of prefrontal and parietal regions or to be more precise, of brain regions in the areas BA 46, BA 6, and BA 40.

The reported association between the bold response during a *n*-back task and the −703 G/T SNP relies on a small group of $n = 5$ TT carriers. This is definitely the lower end of what is tolerable in an fMRI task. However, it has to be kept in mind that the prevalence of the TT genotype in the population is less than 5%. Therefore, a higher power can only be obtained by testing subjects after an a priori genotyping in hundreds of subjects as done in the Reuter et al. (2007a) study and not by genotyping the subjects post hoc. On the other hand, it is plausible that we rather expect a small subgroup of the population, here the TT carriers, to show extraordinary behaviour (impaired executive control) than to expect such behaviour in a large proportion of the population (carriers of at least one G allele). Unfortunately, we did not control for IQ differences across genotype groups. This is a shortcoming that has to be kept in mind in a replication study.

The present study demonstrates the usefulness of a genetic imaging approach in order to investigate the biological basis of cognitive processes. The combination of fMRI and molecular genetics simultaneously provides information on the neuroanatomical regions and the neurotransmitter systems involved, and moreover explains individual differences in WM that cannot be detected by the behavioural data.

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