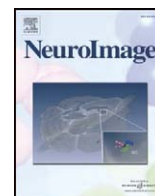




Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: Evidence from a genetic imaging study

Christian Montag^{a,*}, Martin Reuter^a, Beate Newport^b, Christian Elger^{b,c}, Bernd Weber^{b,c}

^a Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9 D-53111 Bonn, Germany

^b Department of Epileptology, University Hospital of Bonn, Germany

^c Department for NeuroCognition, Life & Brain Center, Bonn, Germany

ARTICLE INFO

Article history:

Received 14 March 2008

Revised 5 June 2008

Accepted 10 June 2008

Available online xxxx

ABSTRACT

Mounting evidence shows that the brain derived neurotrophic factor (BDNF) plays a crucial role in synaptic plasticity. Due to its potential involvement in psychiatric diseases like depression and anxiety disorders BDNF lately became a major target in research. A functional variant of the BDNF gene – the BDNF Val66Met polymorphism – is of particular interest, because it influences the BDNF secretion which is followed by signaling at the TrkB receptor leading to dendritic growth of neurons. Findings from genetic association studies in humans yield heterogeneous results with respect to the question of which allele represents a potential risk factor for an affective disorder. Although structural MRT studies revealed that the 66Met variant is associated with smaller hippocampi and could therefore present the risk allele, fMRI studies investigating the processing of emotion with respect to the BDNF Val66Met polymorphism are lacking.

N=37 healthy female subjects participated in an fMRI experiment with an affective startle reflex paradigm. Carriers of the 66Met variant showed stronger amygdala activation in the right hemisphere in response to emotional stimuli compared to neutral stimuli. The results of this study add to growing literature, showing that it is the 66Met, which is associated with higher trait anxiety.

© 2008 Elsevier Inc. All rights reserved.

Introduction

The protein *brain derived neurotrophic factor* (BDNF) plays a crucial role for synaptic plasticity and affects the growth and survival of neurons (see reviews by Groves, 2007; Martinowitch et al., 2007). A long tradition with a focus on monoaminergic transmitters in exploring the biological underpinnings of depression and anxiety disorders has been enriched by BDNF. A link of BDNF to depression was established e.g. through postmortem analyses reporting that depressive patients who underwent treatment with antidepressive drugs showed higher levels of BDNF in contrast to healthy participants. Patients without antidepressive treatment on the other hand exhibited lower levels of BDNF compared to healthy subjects (Dwivedi et al., 2003; Karege et al., 2002). But the conclusion that lack of BDNF plays a causal role in developing depression does not seem to be the case,

as several animal studies demonstrated that the infusion of BDNF in the ventral tegmental area and the nucleus accumbens in the mammalian brain can lead to depressive-like-behavior (Eisch et al., 2003; Berton et al., 2006). Now there is increasing agreement among researchers that BDNF potentially acts as a mediator of antidepressive effects in treating depression by inducing neurogenesis (once again see reviews by Groves, 2007; Martinowitch et al., 2007). Due to the heterogeneity of BDNF effects the Yin and Yang hypothesis of BDNF came up (Lu et al., 2005): positive effects of BDNF have been associated mainly with signaling of the *matureBDNF* form via the tyrosine kinase B receptor (TrkB) on the hippocampus level, which is followed by dendritic spine growth. The precursor molecule of *matureBDNF* – called *proBDNF* – has been associated with atrophic effects via signaling at the p75^{NTR} receptor in the mesolimbic reward system of the mammalian brain (Zagrebelsky et al., 2005).

On the molecular genetic level a prominent target on the BDNF gene (MIM 113505) is the BDNF Val66Met polymorphism (rs6265), a single nucleotide polymorphism (SNP) on human chromosome 11p14.1 leading to an exchange of amino acids from valine (Val) to methionine (Met). A seminal knock-in-mice study (Chen et al., 2006) showed that the homozygous

* Corresponding author. Fax: +49 228 73 62331.

E-mail address: christian.montag@uni-bonn-diff.de (C. Montag).

66Met variant is associated with an altered BDNF secretion and higher anxious behavior. The transfer of these results to humans revealed heterogeneous results. Association studies using self-report-measures for trait anxiety revealed associations between the 66Val but also the 66Met allele with higher trait anxiety (Lang et al., 2005; Sen et al., 2003; Jiang et al., 2005). Studies with clinical samples did not dissolve this heterogeneity. Studies in elderly Chinese (Hwang et al., 2006) and in Japanese patients with major depression showing suicidal and psychotic symptoms found associations with the 66Met allele, other studies could not find that link (Hong et al., 2003; Tsai et al., 2003; Choi et al., 2006). Recently, a study by Montag et al. (unpublished data) demonstrated in a large sample of Caucasians that it might be the occurrence of not one but two Met alleles, which might be associated with higher trait anxiety, therefore supporting for the first time the findings from animal research (Chen et al., 2006). The investigation of the homozygous 66Met allele variant and its association with anxiety is extremely difficult because of the low prevalence of homozygote 66Met carriers (only 2–3% in the Caucasian population). The heterozygous Val/Met genotype occurs in the Caucasian population with a prevalence of 20–30% (Shimizu et al., 2004).

A further step to investigate the association of the 66Met and the 66Val allele with higher anxiety would be the use of an experimental approach to get away from the very important – but taken alone single sided – genetic association studies without referring to the neuronal response to emotional stimuli. Up to now genetic fMRI studies including the BDNF Val66Met polymorphism only examined the influence of this SNP on working memory (Hariri et al., 2003), but never before investigated the processing of emotional information. Although findings with respect to BDNF Val66Met and cognitive functions are inconsistent as well, it seems to be again the 66Met allele, which is conspicuous due to associations with impaired working memory and consolidation processes of information to long term memory (Egan et al., 2003; Miyajima et al., 2008). As emotional dysregulation represents a key element of affective disorders this study tries to close this gap.

A well established paradigm to examine the processing of the emotions fear and anxiety is the affective startle reflex modulation. In this paradigm pictures with pleasant, unpleasant and neutral content are shown. While viewing the pictures an acoustic pulse (e.g. a white noise) is administered eliciting a startle reflex in the subjects. Interestingly, the startle, which occurs as a response to the noise, is modulated by environmental emotional cues. The startle is attenuated when viewing pleasant pictures and it is potentiated during the processing of unpleasant pictures. With respect to the revised Reinforcement Sensitivity Theory (RST) by Gray and McNaughton (2000), exploring the neuroanatomical and molecular processes underlying anxiety and fear, this paradigm presents a good measure for individual differences in trait anxiety (Hawk and Kowmas, 2003; Caseras et al., 2006; Montag et al., in press), which is called the Behavioral Inhibition System (BIS). The psychological construct BIS is triggered through all kinds of conflicts and novel stimuli, with which an organism is confronted. The organism stops or inhibits its current activity in a situation of conflict and shifts attention to dissolving it. Uncertainty about dissolving the conflict via approach (through activation of the Behavioral Activation System) or avoidance (through activation of the

Fight Flight Freezing System) is followed by the emotion anxiety. Viewing of a pleasant picture while listening to the white noise therefore represents an approach–avoidance conflict, the same constellation with an unpleasant picture equals an avoidance–avoidance situation. Personality psychologists tried to measure individual differences in the BIS system with self-report questionnaire (e.g. Carver and White, 1994), although it is questionable if it is possible to gain direct access via introspection to those mostly unconsciously driven processes (Smillie et al., 2006). Therefore, it might be a better approach to measure interindividual differences in neuronal response to emotional stimuli depending on candidate gene loci, which functionally influence protein synthesis and have been associated with a special phenotype like anxious behavior in animals and humans before (Reuter and Montag, in press; Smillie, in press).

Due to a small overweight of studies reporting associations of the 66Met allele with anxiety and depression we predicted that carriers of at least one 66Met allele react with a higher amygdala activity to all emotional startle conditions. As the revised RST postulates that anxiety is elicited through all kinds of conflicts (also approach–approach conflicts!) or through the confrontation with novel stimuli, we hypothesised a higher anxiety related amygdala BOLD signal in the conflicting pleasant and unpleasant startle conditions. With respect to the problems of measuring the startle reflex of the lid in an fMRI setting (which is now possible via infrared techniques, but we had no access to this new technology), we could not record the startle reflex. Until now two studies have already shown that this well established paradigm from psychophysiology also works in an fMRI setting (Anders et al., 2004; Eippert et al., 2007).

In a pilot study we already showed that interindividual differences in the BIS system correlate with the startle reflex in the pleasant and unpleasant picture pulse condition of the affective startle reflex modulation paradigm (Montag et al., in press). Therefore we decided against establishing a sole picture without startle condition. Moreover, the experiment – now lasting 40 min – would have needed nearly twice the time if a picture alone condition would have been added. This would have been too much stress for the participants from our point of view. With respect to Gray's revised RST the sole novelty of a stimulus can elicit a conflict. In addition the occurrence of two stimuli presented simultaneously (conflict condition) is an alternative way to trigger the BIS system besides the novelty aspect (picture alone condition). By using both, the novelty aspect of the pictures and the conflict aspect of combining startle and pictures we assumed to potentiate the activity of BIS related neuroanatomical structures.

Several studies showed that a key structure for BDNF action is the hippocampus. A recent study showed that carriers of the Met allele have an 11% reduced hippocampus volume, which could be a consequence of an altered BDNF secretion in carriers of that allele variant (Bueller et al., 2006). When Jeffrey Gray started his RST research in the 1970s he derived from his studies using anxiolytics in animals (Gray, 1972), that the septo-hippocampal system is a key structure in the genesis of the emotion anxiety. The revised RST still proposes that the septo-hippocampal system remains to be important for anxious behavior, although Gray and McNaughton (2000) included several other structures including the amygdala, which together built the anxiety network BIS. Concluding from these studies, the hippocampus

could also be differentially activated in BDNF 66Met+ and BDNF 66Met- carriers while processing emotional contents. In line with a hypothesised higher reactivity of the amygdala in sight of emotional stimuli also the hippocampus could react with a higher BOLD signal in response to emotional stimuli.

Methods

Participants

37 healthy Caucasian female participants from Bonn, Germany participated in the fMRI study (Age: 23; SD=3; Range 19–41). All participants did not report a psychopathological/neurological disorder in a standardized questionnaire. In order to control for possible gender effects, we only invited female participants. As participants were mainly recruited in psychology classes, which are dominantly attended by females, not enough males could have been recruited for this study. All participants provided buccal cells from which the BDNF Val66Met polymorphism could be genotyped. Participants got 12 Euro and course credits for participation in this study. After participation every participant was thanked and debriefed. The study was approved by the medical ethics committee of the University of Bonn.

Participants were placed in the Siemens Avanto 1.5 T scanner. Participants wore earphones (NordicNeurolab, Bergen, Norway), over which the startle probes were binaurally administered. The pictures were shown in the fMRI scanner via Video goggles (NordicNeurolab, Bergen, Norway).

35 coronal slices perpendicular to the mediotemporal lobe with a matrix size of 64*64 and a field of view of 250 mm*250 mm were collected at 1.5 T (Avanto, Siemens, Erlangen, Germany). We acquired ~770 T2*-weighted gradient echo EPI-scans with the following parameters: slice-thickness 5.0 mm, interslice gap: 0.5 mm; TR: 3 s; TE: 40 ms; phase encoding direction: head>foot.

The pulse alone condition consisted of 24 startle probes (white noise, 106 dB, 35 ms duration, 5 ms risetime) with an inter-stimulus-interval (ISI) from 15. Before it was tested by several persons that the white noise is well detectable against the background noise of the Avanto scanner. The ASRM paradigm consisted of 24 pleasant, 24 unpleasant and 24 neutral pictures (duration 6 s, onset of startle probe randomized 2.5–5.5 after onset of the pictures) and an ISI from 15 s. The onset of the startle probe was balanced over the different picture conditions. Conditions were administered in randomized order.

Pictures used in the emotional startle paradigm were taken from the *International Affective Picture System (IAPS)* (70). The affectively valenced pictures were chosen on the basis of affective valence ratings by a female normative sample. Animals, baby and family photos were chosen as pleasant stimuli. Neutral stimuli were e.g. a power outlet or a hair dryer. Unpleasant stimuli consisted of pictures depicting fear or threat, such as weapons or injured victims at a crime scene.

fMRI data analysis

The fMRI data analysis was performed using Statistical Parametric Mapping 5 (SPM5, www.fil.ion.ucl.ac.uk/spm/). Preprocessing included slice timing, realignment with

unwarping, normalisation to an EPI-template (re-sampled voxel size after normalisation 3*3*3 mm) and smoothing with an 8 mm Gaussian kernel. Seven vectors of onset times were defined for the following conditions: i) neutral images; ii) pleasant images; iii) unpleasant images, iv) fixation with startle probe, v) neutral images with startle probe, vi) pleasant images with startle probe and vii) unpleasant images with startle probe. The first three regressors were modelled at the onset of the image presentation with a duration of 6 s, the regressors for the startle probes were modelled as instantaneous events. To model the BOLD time course in each voxel these onset vectors were convolved with the SPM5 canonical hemodynamic response function (HRF) and its temporal derivative. For each subject, parameter images for the contrasts of each condition were generated and were then subjected to a second-level random effects analysis using a factorial design option in SPM5 with emotion (neutral, positive, negative) as a within-subject factor and genotype (BDNF Met+, Met-) as between-subject factor. An inclusion threshold of $p < 0.001$ uncorrected with an extent threshold of at least ten contiguous voxels was applied. The *MarsCoil*-toolbox for SPM 5 (Reimold et al., 2006) was used to label the clusters.

For the region of interest analysis, a mask was built including the left and right amygdala based on the SPM toolbox “wfu-pickatlas” (Maldjian et al., 2003). For the ROI analysis a corrected threshold was applied with $p < 0.05$. In the unpleasant vs. pleasant contrast an uncorrected threshold of $p < 0.05$ was used.

Genotyping

DNA was extracted from buccal cells. 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 BDNF Val66Met polymorphism was performed by real time PCR using fluorescence melting curve detection analysis by means of the Light Cycler System 1.5 (Roche Diagnostics, Mannheim, Germany). The primers and hybridization probes (TIB MOLBIOL, Berlin, Germany) and the PCR protocol for BDNF Val66Met are as follows:

forward primer: 5'-ACTCTGGAGAGCGTGAATGG-3';
reverse primer: 5'-CCAAAGGCACCTTGACTACTGA-3';
anchor hybridization probe: 5'-LC640-CGAACACATGATA GAAGAGCTGTT-phosphate-3';
sensor hybridization probe: 5'-AAGAGGCTTGACATCATTGG-CTGACACT-fluorescein-3'.

The PCR run comprised 50 cycles of denaturation (95 °C, 0 s, ramp rate 20 °C s⁻¹), annealing (55 °C, 10 s, ramp rate 20 °C s⁻¹), acquisition of the fluorescence signal (55 °C, 1 s, ramp rate 20 °C s⁻¹) and extension (72 °C, 12 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 Val allele was 58.5 °C and 63.8 °C for the Met allele.

Results

Effect of the startle probes

The startle probes only elicited activation in the bilateral primary auditory cortex. No additional activation was observed independent of the emotional context of their presentation.

Main effect of emotion

Table 1 gives an overview of the areas which showed a main effect of emotion, including the right amygdala, the left and right inferior frontal gyrus and the bilateral inferior parietal gyrus. Fig. 1 shows sections through the medial temporal lobe for the contrasts pleasant vs. neutral (Fig. 1A) and unpleasant vs. neutral (Fig. 1B) independent of genotype. In both contrasts stronger activation in the amygdala was observed for the emotional in comparison to the neutral stimuli with only right-lateralized activation in the unpleasant vs. neutral contrast and bilateral activation in the pleasant vs. neutral contrast. No activation was observed for the opposite contrast.

Interaction of emotion and genotype in the amygdala

To investigate the influence of the 66Met polymorphism on emotional perception and based on previous results, a region of interest analysis including the bilateral amygdala was performed. A strong modulatory effect of the 66Met polymorphism was observed in the pleasant vs. neutral contrast in the right amygdala with stronger activation in the 66Met+ allele carriers (T -score=3.38, $p<0.05$ corrected; Fig. 2A). This

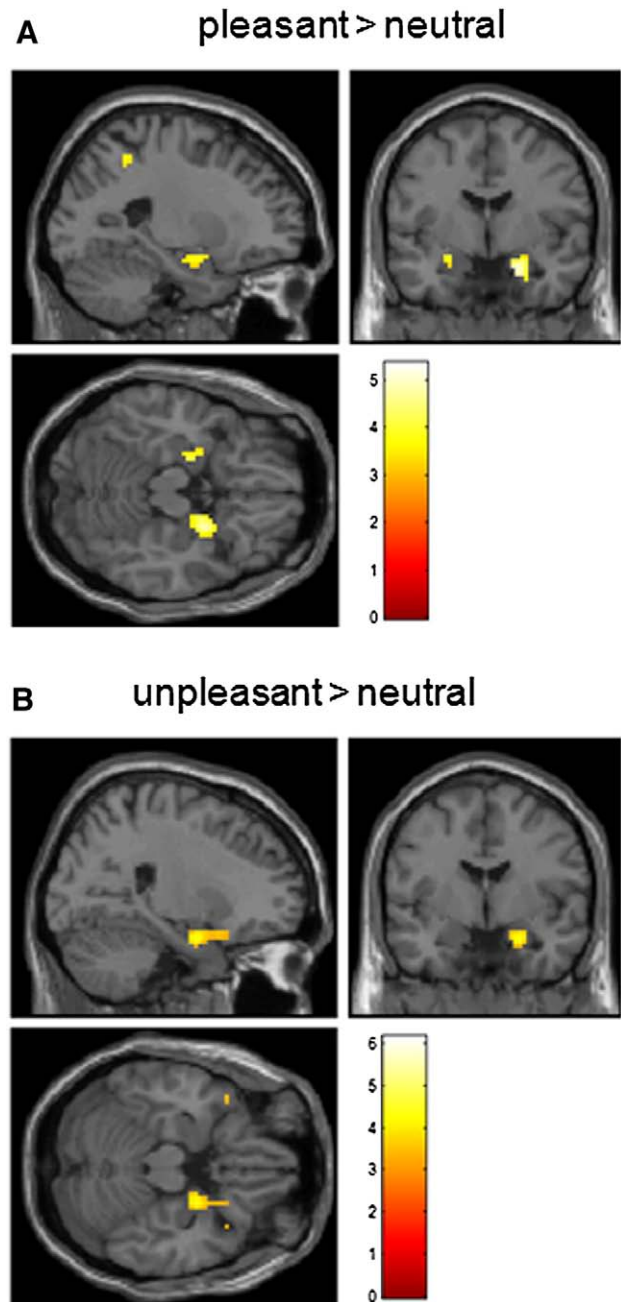


Fig. 1. Section through the local maximum in the amygdala of the contrast pleasant vs. neutral [max. activation at 21/–4/–20] (A) and unpleasant vs. neutral [24/–4/–17] (B) independent of genotype ($p<0.001$, 10 voxel cluster threshold).

effect was not as strong in the unpleasant vs. neutral contrast (T -score=2.23, $p<0.05$ uncorrected; Fig. 2B).

Discussion

The aim of the present study was to investigate the influence of the functional BDNF Val66Met polymorphism on the processing of emotional stimuli. Evidence from a seminal knock-in-mice study suggests (Chen et al., 2006) that the 66Met allele leads to higher trait anxiety. The transfer of these results to human studies yielded heterogeneous evidence so far, with a small overweight of studies showing that it is rather the 66Met than the 66Val allele being associated with anxiety and depression (see review by Groves, 2007). Strong evidence for

Table 1

Overview of significantly activated clusters independent of genotype in the respective contrasts

Region	Peak TAL coordinates [X/Y/Z]	Cluster size	F-value
<i>Main effect of emotion</i>			
R. mid. temp. gyrus	50/–70/1	141	21.06
R. inf. parietal gyrus	45/–45/41	123	17.71
L. mid. occ. gyrus	–45/–75/7	76	14.31
R. amygdala	22/–4/–20	64	13.60
L. inf. parietal gyrus	–50/–59/47	27	12.74
L. inf. frontal gyrus	–48/10/16	32	12.09
R. postcentral gyrus	15/–32/65	50	12.01
L. paracentral gyrus	–15/–23/65	66	11.08
R. angular gyrus	39/–65/47	13	10.28
R. inf. frontal gyrus	45/10/27	15	9.60
L. supramarginal gyrus	–62/–54/25	14	9.17
L. mid. frontal gyrus	–30/11/41	10	8.84
			<i>T-value</i>
<i>Unpleasant > Neutral</i>			
R. mid. temporal gyrus	50/–70/1	202	6.16
L. mid occ. gyrus	–45/–75/7	125	5.34
L. inf. parietal gyrus	–24/–44/49	41	4.80
R. amygdala	24/–4/–17	54	4.37
R. inf. frontal gyrus	45/10/27	60	4.36
R. sup. temp. gyrus	42/16/–24	26	4.20
L. insula	–39/17/–11	60	4.06
<i>Pleasant > Neutral</i>			
R. mid. temporal gyrus	51/–64/9	123	5.36
R. amygdala	21/–4/–20	97	4.94
L. hippocampus	–21/–9/–15	26	4.10
L. mid. occipital gyrus	–50/–73/4	52	3.75
L. sup. parietal gyrus	–24/–47/47	10	3.65

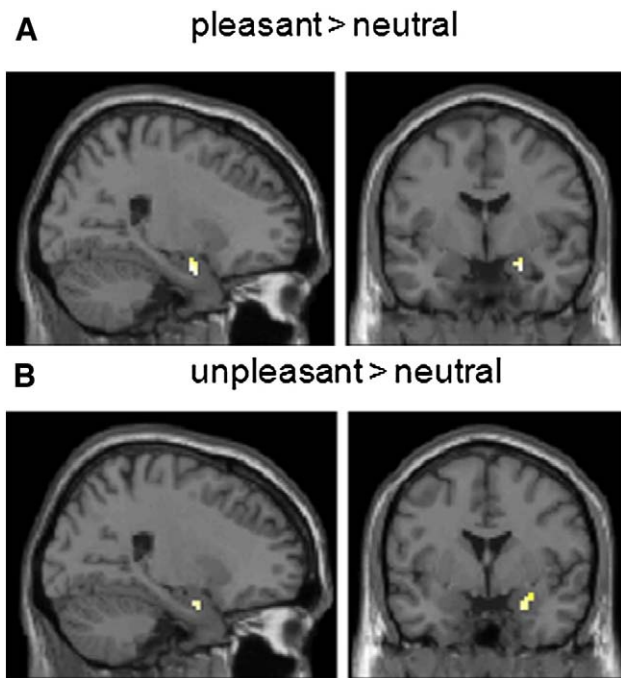


Fig. 2. Sections of areas which showed stronger activation in the amygdala in the Met+ group in comparison to the Met- group in the contrast of pleasant vs. neutral images [max. activation at 24/–5/–19] (A) and unpleasant vs. neutral images [25/1/–18] (B). Note that the statistical threshold in (B) was set to 0.05 (corrected for multiple comparisons) in the pleasant vs. neutral contrast, but uncorrected in the unpleasant vs. neutral contrast. No activation was observed in the opposite contrast.

this trend comes from studies using voxel based morphometry (VBM) to explore the impact of the BDNF Val66Met polymorphism on the hippocampal region (Pezawas et al., 2004; Bueller et al., 2006). Carriers of at least one 66Met allele showed a significant reduction of the hippocampus compared to the homozygous 66Val carriers. With respect to findings showing that stress can lead to atrophic effects in the hippocampus, which is discussed to play an important role in depressive-like-behavior (e.g. Joëls et al., 2008; Zhao et al., 2007), findings from brain volumetry suggest that carriers of the 66Met allele may carry a predisposition for depression and anxiety disorders. A recent study reported, by comparing healthy and depressive subjects, that carriers of at least one 66Met allele showed significant smaller hippocampi in both samples, therefore building the bridge between clinical and healthy samples (Frodl et al., 2007). Interestingly, studies are lacking which investigate the influence of the BDNF Val66Met polymorphism on the processing of emotions in an fMRI setting. Besides the mentioned structural MRI studies, only one fMRI study exists exploring the impact of BDNF Val66Met on working memory, showing that the carriers of the 66Met allele show impaired working memory and consolidation processes (Egan et al., 2003).

We hypothesised that carriers of the 66Met allele react to emotional stimuli in contrast to neutral stimuli with a significant higher amygdala activity compared to the homozygous 66Val group. Our results support this hypothesis demonstrating for the first time that carriers of the 66Met+ group react stronger to emotional cues than the 66Met-group. Amygdala activity of the 66Met+ group is high both in the pleasant as well as in the unpleasant picture condition compared to the neutral condition, which could be explained

very well with the revised Reinforcement Sensitivity Theory (RST) by Gray and McNaughton (2000). The simultaneous occurrence of two stimuli could lead to a conflict through the basal “decision” of processing the pleasant/unpleasant picture or the aversive startle probe (Montag et al., in press). The revised RST postulates that the anxiety related construct BIS (Behavioral Inhibition System) is triggered through such conflicts. A conflict elicits uncertainty, which gives way for the emotion anxiety. As the participants in our study saw the IAPS pictures for the first time in a fairly inhospitable surrounding – the fMRI scanner – these BIS mechanisms could even be triggered stronger. Particularly the revised RST postulates that also the novelty of a situation is crucial for the rise of uncertainty. With respect to a potentiating or conflict eliciting effect of the startle we included the onset of the startles as regressors in our model, but we could not find an effect of the startle on any other region than the auditory cortex. This may be due to a lack of statistical power. With respect to these results we argue that the main influence of the BDNF Val66Met polymorphism in the present study seems to refer not to the processing of (emotional) conflict situations, but to the processing of emotional stimuli per se.

Besides the amygdala another key area of the BIS in the mammalian brain and also a major target of BDNF signaling is the hippocampus (Gray and McNaughton, 2000). Interestingly BDNF has been considered to be a very important factor in both structures of the mammalian brain (Monfils et al., 2007; Krause et al., 2008; Martinowitch et al., 2007), although findings for the involvement of BDNF in consolidation processes in the amygdala mainly come from animal research. We could not detect interindividual differences in the BOLD signal of the hippocampus depending on the BDNF Val66Met polymorphism while the emotional cues were processed by the participants of our study. The nonfinding of differential hippocampus activation does not mean that the hippocampus is not important for the processing of anxiety. It could be differentially activated in situations, where memory and consolidation processes are more important than in our paradigm which did not focus on cognitive but on affective processing. This could be e.g. be the case in the consolidation of unpleasant situations.

Shortcomings of the present study are that we have not included a picture alone condition and that positive pictures were not balanced according to arousal ratings. The latter point is difficult because only erotic pictures elicit strong arousal and this is more in men than in woman. However, our study consisted only of women.

Taken together, this study shows for the first time the influence of the BDNF Val66Met polymorphism on emotional processing in an fMRI study. Further studies are needed to elucidate the mechanism of BDNF in higher cognitive functions especially in respect to emotional memories.

References

- Anders, S., Lotze, M., Erb, M., Grodd, W., Birbaumer, N., 2004. Brain activity underlying emotional valence and arousal: a response-related fMRI study. *Hum. Brain Mapp.* 23, 200–209.
- Berton, O., McClung, C.A., DiLeone, R.J., Krishnan, V., Renthall, W., Russo, S.J., Graham, D., Tsankova, N.M., Bolanos, C.A., Rios, M., Monteggia, L.M., Self, D.W., Nestler, E.J., 2006. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864–868.
- Bueller, J.A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., Zubieta, J.K., 2006. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biol. Psychiatry* 59, 812–815.

- Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *J. Pers. Soc. Psychol.* 67, 319–333.
- Caseras, F.X., Fullana, M.A., Riba, J., Barbanjo, M.J., Aluja, A., Torrubia, R., 2006. Influence of individual differences in the Behavioral Inhibition System and stimulus content (fear versus blood-disgust) on affective startle reflex modulation. *Biol. Psychology* 72, 251–256.
- Chen, B., Dowlatsahi, D., MacQueen, G.M., Wang, J.F., Young, L.T., 2001. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* 50, 260–265.
- Chen, Z.Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* 314, 140–143.
- Dwivedi, Y., Rizavi, H.S., Conley, R.R., Roberts, R.C., Tamminga, C.A., Pandey, G.N., 2003. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch. Gen. Psychiatry* 60, 804–815.
- Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112, 257–269.
- Eisch, A.J., Bolanos, C.A., de Wit, J., Simonak, R.D., Pudiak, C.M., Barrot, M., Verhaagen, J., Nestler, E.J., 2003. Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression. *Biol. Psychiatry* 54, 994–1005.
- Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., Anders, S., 2007. Regulation of emotional responses elicited by threat-related stimuli. *Hum. Brain Mapp.* 28, 409–423.
- Frodl, T., Schüle, C., Schmitt, G., Born, C., Baghai, T., Zill, P., Bottlender, R., Rupprecht, R., Bondy, B., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2007. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch. Gen. Psychiatry* 64, 410–416.
- Gray, J., 1972. *The Psychology of Fear and Stress*. McGraw-Hill.
- Gray, J., McNaughton, N., 2000. *The Neuropsychology of Anxiety*. Oxford Press, Oxford.
- Groves, J.O., 2007. Is it time to reassess the BDNF hypothesis of depression? *Mol. Psychiatry* 12, 1079–1088.
- Hariri, A.R., Goldberg, T.E., Mattay, V.S., Kolachana, B.S., Callicott, J.H., Egan, M.F., Weinberger, D.R., 2003. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J. Neurosci.* 23, 6690–6694.
- Hawk Jr., L.W., Kowmas, A.D., 2003. Affective modulation and prepulse inhibition of startle among undergraduates high and low in behavioral inhibition and approach. *Psychophysiol.* 40, 131–138.
- Hong, C.J., Huo, S.J., Yen, F.C., Tung, C.L., Pan, G.M., Tsai, S.J., 2003. Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology* 48, 186–189.
- Hwang, J.P., Tsai, J.S., Hong, C.J., Yang, C.H., Lirng, J.F., Yang, Y.M., 2006. The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol. Aging* 27, 1834–1837.
- Jiang, X., Xu, K., Hoberman, J., Tian, F., Marko, A.J., Waheed, J.F., et al., 2005. BDNF variation and mood disorders: a novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. *Neuropsychopharmacology* 30, 1353–1361.
- Joëls, M., Krugers, H., Karst, H., 2008. Stress-induced changes in hippocampal function. *Prog. Brain Res.* 167, 3–15.
- Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., Aubry, J.M., 2002. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.* 109, 143–148.
- Krause, S., Schindowski, K., Zechel, S., von Bohlen und Halbach, O., 2008. Expression of trkB and trkC receptors and their ligands brain-derived neurotrophic factor and neurotrophin-3 in the murine amygdala. *J. Neurosci. Res.* 86, 411–421.
- Lang, U.E., Hellweg, R., Kalus, P., Bajbouj, M., Lenzen, K.P., Sander, T., et al., 2005. Association of a functional BDNF polymorphism and anxiety-related personality traits. *Psychopharmacology (Berl)* 180, 95–99.
- Lu, B., Pang, P.T., Woo, N.H., 2005. The yin and yang of neurotrophin action. *Nat. Rev. Neurosci.* 6, 603–614.
- Maldjian, J.A., Laurienti, P.J., Burdette, J.B., Kraft, R.A., 2003. An Automated Method for Neuroanatomic and Cytoarchitectonic Atlas-based Interrogation of fMRI Data Sets. *NeuroImage* 19, 1233–1239.
- Martinowitch, K., Husseini, M., Bai, L., 2007. New insights into BDNF function in depression and anxiety. *Nat. Neurosci.* 10, 1089–1093.
- Monfils, M.H., Cowansage, K.K., LeDoux, J.E., 2007. Brain-derived neurotrophic factor: linking fear learning to memory consolidation. *Mol. Pharmacol.* 72, 235–237.
- Miyajima, F., Ollier, W., Mayes, A., Jackson, A., Thacker, N., Rabbitt, P., Pendleton, N., Horan, M., Payton, A., 2008. Brain-derived neurotrophic factor polymorphism Val66Met influences cognitive abilities in the elderly. *Genes Brain Behav.* 7, 411–417.
- Montag, C., Buckholz, J.W., Hartmann, P., Merz, M., Burk, C., Hennig, J., Reuter, M., in press. COMT genetic variation impacts fear processing: psychophysiological evidence. *Behav. Neurosci.* 122.
- Pezawas, L., Verchinski, B.A., Mattay, V.S., Callicott, J.H., Kolachana, B.S., Straub, R.E., Egan, M.F., Meyer-Lindenberg, A., Weinberger, D.R., 2004. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J. Neurosci.* 10, 10099–10102.
- Reimold, M., Slifstein, M., Heinz, A., Müller-Schauenburg, W., Bares, R., 2006. Effect of spatial smoothing on t-maps: arguments for going back from t-maps to masked contrast images. *J. Cereb. Blood Flow Metab.* 26, 751–759.
- Reuter, M., Montag, C., in press. Switching the perspective: From neuroscience to personality. *Eur. J. Pers.*
- Sen, S., Nesse, R.M., Stoltenberg, S.F., Li, S., Gleiberman, L., Chakravarti, A., et al., 2003. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology* 28, 397–401.
- Shimizu, E., Hashimoto, K., Iyo, M., 2004. Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. *Am. J. Med. Genetics B Neuropsychiatr. Genet.* 126B, 122–123.
- Smillie, L.D., Pickering, A.D., Jackson, C.J., 2006. The new reinforcement sensitivity theory: implications for personality measurement. *Personality and Social Psychology Review* 10, 320–335.
- Smillie, L.D., in press. What is reinforcement sensitivity? Neuroscience paradigms for approach–avoidance process theories of personality. *Eur. J. Pers.* 22.
- Zagrebelsky, M., Holz, A., Dechant, G., Barde, Y.A., Bonhoeffer, T., Korte, M., 2005. The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. *J. Neurosci.* 25, 9989–9999.
- Zhao, H., Xu, H., Xu, X., Young, D., 2007. Predatory stress induces hippocampal cell death by apoptosis in rats. *Neurosci. Lett.* 421, 115–120.