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LETTERS TO THE EDITOR

BNDF modulates normal human hippocampal ageing

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Brain-derived neurotrophic factor (BDNF), a neutrophin highly expressed in the hippocampus, has been associated with hippocampal-dependent learning and memory processes.[1] A polymorphism in the *BDNF* (*BDNFval^{66}met; rs6265*) gene causing a valine (val)-to-methionine (met) substitution at codon 66 results in altered intracellular trafficking and packaging of BDNF, and in a reduction of its regulated secretion.[1] *BDNFval^{66}met* genotype predicts variation in human episodic memory, as well as in hippocampal anatomy and function.[1,2] In rats, BDNF-mediated beneficial effects on neuroprotection, memory ability and learning decrease with advancing age.[3] Interestingly, hippocampal activity in humans,[4] as well as the expression of BDNF and its receptor[5] in this region also decrease with age. In line with these findings, we expected that age-related decline of hippocampal function would be modulated by genetically determined variation in BDNF function, such that *BDNF*-met allele carriers (expressing diminished regulated secretion of BDNF) would show a more pronounced decrease in memory-dependent hippocampal activity with advancing age relative to *BDNF*-val/val individuals.

We studied 125 healthy, Caucasian participants (age: 19–85 years, 65 females, see Supplementary Materials, Table 1) during the performance of a simple declarative memory task that included incidental encoding and retrieval phases using whole-brain BOLD fMRI (blood–oxygen-level-dependent functional magnetic resonance imaging), as described previously.[6] Participants were genotyped for *BDNFval^{66}met*, *apolipoprotein E* and *Catechol-O-methyltransferase* polymorphisms.[6] On the basis of *BDNFval^{66}met* genotype, they were subdivided into met-carriers (met/met = 9; val/met = 36) and val/val homozygote individuals ($n = 80$). Demographic features (IQ, education, age, gender and handedness), *apolipoprotein-E* and *catechol-O-methyltransferase* polymorphism genotypes, and retrieval performance (accuracy and reaction time) were not significantly different across *BDNFval^{66}met* genotype groups. Random-effects general linear model simple regressions with age as a predictor on encoding > fixation and retrieval > fixation individual activation maps were computed in SPM5 (http://www.fil.ion.ucl.ac.uk/spm). On the basis of our *a priori* hypothesis for an age-by-*BDNFval^{66}met* interaction in hippocampal function, we extracted and analyzed BOLD signal change from the most significant clusters in left and right hippocampal regions, as identified by WFU-PickAtlas (http://www.fmri.wfubmc.edu), for each condition with a statistical threshold of $P < 0.05$ corrected for multiple comparisons using a false discovery rate with $\alpha = 0.05$. The coefficients of the correlations between signal-change and age were then compared between *BDNFval^{66}met* groups using one-tailed Fisher's *r*-to-*z*′ transform. To ensure that these changes were not driven by *BDNFval^{66}met* effects on structural changes in the hippocampus, we analyzed a subsample (17 met-carriers, 35 val/val; matched for demographics, and behavioral performance, *apolipoprotein-E* and *catechol-O-methyl transferase* polymorphism genotypes, see Supplementary Materials, Table 2) that also underwent three-dimensional structural magnetic resonance imaging using a T1-weighted SPGR sequence.[2] Structural images were segmented, spatially normalized and modulated using the unified segmentation approach in SPM5. Hippocampal volumes were calculated from the resulting grey-matter images using WFU-PickAtlas. Multiple regressions on hippocampal activations for each condition, with age and hippocampal volume as covariates, were than computed and partial correlation coefficients were compared as above.

There was a significant age-related decline in activation of posterior hippocampal region bilaterally during encoding and retrieval phases (see Supplementary Materials, Table 3). When analyzed by *BDNFval^{66}met* genotype, met-carriers showed a significantly steeper slope in age-related decline in hippocampal activation bilaterally during encoding and retrieval phases relative to val/val individuals (Figure 1; Supplementary Materials, Table 4). These results remained significant in the hippocampal region bilaterally during encoding and in the left hippocampal region during retrieval, even after using the hippocampal volume as a covariate (see Supplementary Materials). We also found increased bilateral inferior frontal activity with increasing age during retrieval (see Supplementary Materials, Table 5, Figure S1A), possibly reflecting a compensatory response to maintain performance.[4] Met-carriers showed greater activation in this region relative to val/val individuals, but there was no age by *BDNFval^{66}met* interaction (see Supplementary Materials, Figure S1).

Consistent with our hypothesis, we found that *BNDFval^{66}met* genotype modulates age-related changes in hippocampal function. Met-carriers

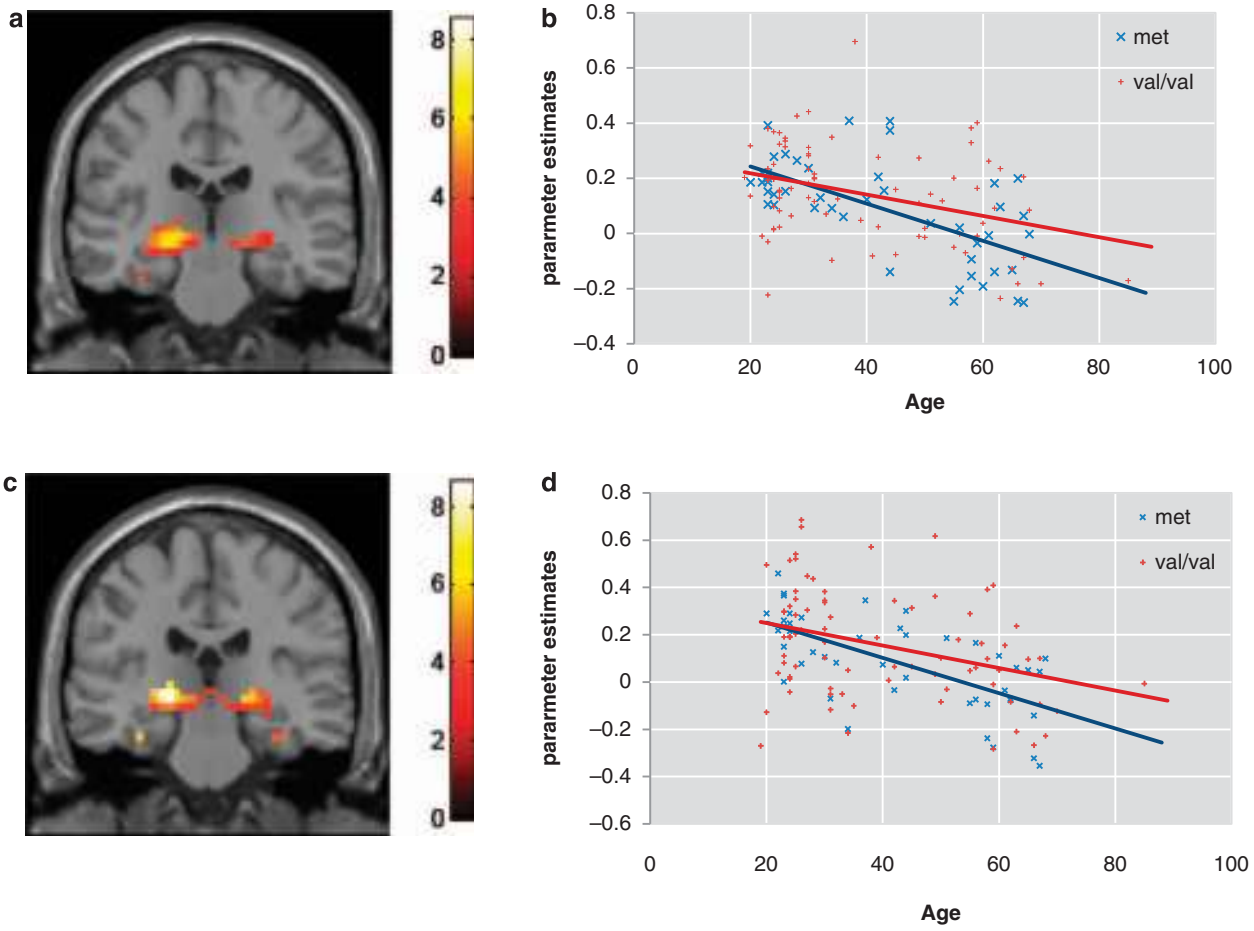

Figure 1 Effect of *BDNFval*^{66}*met* polymorphism on age-related decline in hippocampal activation during a simple declarative memory task. Thresholded coronal ($Y=-22$) statistical *t*-maps ($P<0.05$; FDR corrected) overlaid on the MNI brain template show age-related decline in hippocampal activation during the encoding (**a**) and retrieval (**c**) phases. Met-allele carriers ($n=45$) show a steeper negative correlation between age and hippocampal activity during encoding (**b**) and retrieval (**d**) phases of the task relative to val/val individuals ($n=80$). Scatterplots show relationship between parameter estimates of the BOLD (blood–oxygen-level dependent) response (measured in arbitrary units) in the left-hippocampus during encoding (**b**) and retrieval phase (**d**) and age (in years) for each BDNFval^{66}met genotype group. MNI, Montreal Neurological Institute.

showed a greater age-related decline in hippocampal activation during both encoding and retrieval tasks relative to val/val individuals, and this effect was independent of any potential structural[2] or performance differences.[6]

These data are in line with earlier evidence for an effect of *BNDFval*^{66}*met* polymorphism on hippocampal anatomy[2] and function.[1,6] Most importantly, they illustrate the modulatory effect of this polymorphism on the trajectory of age-related changes in the neurophysiology underlying episodic memory. The decline of hippocampal function is accelerated in met-carriers relative to val/val individuals, suggesting that the latter may be more resilient to age-related changes in hippocampal-dependent declarative memory. These findings add to evidence for a critical role of genes in the heterogeneity of age-related decline in cognition across individuals.

Conflict of interest

The authors declare no conflict of interest.

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F Sambataro[1], VP Murty[1], HS Lemaitre[1], JD Reed[1], S Das[1], TE Goldberg[2], JH Callicott[1], DR Weinberger[1] and VS Mattay[1]
[1]*Genes, Cognition, and Psychosis Program, Clinical Brain Disorders Branch, National Institute of Mental Health Intramural Research Program, National Institutes of Health, Bethesda, MD, USA and* [2]*Department of Psychology,*

Zucker Hillside Hospital/Feinstein Institute/AECOM, State University of New York at Stony Brook, Stony Brook, NY, USA
E-mail: vsm@mail.nih.gov

References

1 Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A *et al. Cell* 2003; **112**: 257–269.
2 Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE *et al. J Neurosci* 2004; **24**: 10099–10102.
3 Sohrabji F, Lewis DK. *Front Neuroendocrinol* 2006; **27**: 404–414.
4 Murty VP, Sambataro F, Das S, Tan HY, Callicott JH, Goldberg TE *et al. J Cogn Neurosci* 2008; e-pub ahead of print 29 September 2008.
5 Webster MJ, Herman MM, Kleinman JE, Shannon Weickert C. *Gene Expr Patterns* 2006; **6**: 941–951.
6 Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF *et al. J Neurosci* 2003; **23**: 6690–6694.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Increased levels of circulating insulin-related peptides in first-onset, antipsychotic naïve schizophrenia patients

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Here, we show that circulating insulin-related peptides are elevated in first-onset schizophrenia subjects, with no relative difference in glucose levels. This suggests that hyperinsulinemia may have a role in the development of schizophrenia, and that measurement of these peptides may have utility in diagnosis or stratification of patients before antipsychotic treatment. Moreover, drugs that improve insulin action may represent a novel treatment strategy.

We, along with others, have identified alterations of metabolic biomarkers in schizophrenia patients, which are indicative of perturbations in glucoregulatory pathways.[1] In addition, schizophrenia patients show increased prevalence of impaired glucose tolerance[2] and metabolic syndrome, irrespective of whether they received antipsychotic treatment.[3] Dysregulation of glucose metabolism is normally accompanied by hyperinsulinemia, because of increased secretory demands on pancreatic β-cells to maintain homeostasis.[4] Insulin is the major glucoregulatory hormone produced in β-cell secretory granules by complete proteolytic cleavage of proinsulin. The mature hormone is released into the circulation in response to elevated glucose levels along with approximately 100 other proteins, including residual proinsulin, the conversion intermediates des31,32-proinsulin and des64,65-proinsulin, C-peptide and chromogranin-like molecules.[5] Here we have investigated whether the circulating levels of these major secreted proteins are altered in schizophrenia patients.

Molecular studies of chronic schizophrenia patients can be confounded since routinely used antipsychotic medications have several side effects, such as dysregulated glucose homeostasis. We circumvented this problem by carrying out analyses of serum and plasma samples from first-onset, antipsychotic naïve patients. Recruitment of such patients is challenging, as large clinics diagnose only 20–30 such patients each year and few centers follow standard operating procedures for sample collection. To achieve adequate numbers of well-characterized first-onset patients, we recruited subjects from four independent clinical centers over 2006–2008. Patients were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for schizophrenia and bipolar disorder. Schizophrenia patients were acutely psychotic (Positive and Negative Symptoms Scale total = 87 ± 16; $n = 66$) and bipolar disorder subjects were euthymic (Young Mania Ratings Scale total = 3.9 ± 4.7, Hamilton Depression scale total = 4.6 ± 5.4; $n = 10$) at the time of sample collection. Euthymic bipolar disorder patients were chosen, as such subjects often experience cognitive deficits similar to those observed in schizophrenia and this can be a potential means of misdiagnosis.[6] Control subjects ($n = 78$) were matched for age, gender, BMI and smoking.

Insulin, proinsulin and des31,32-proinsulin were determined through two-site time-resolved fluorescence assays using combinations of monoclonal antibodies that discriminate between the specific forms of the molecule.[7] C-peptide and chromogranin A were measured using commercially available immunoassays. Insulin, proinsulin, des31,32-proinsulin and C-peptide were found to be present at significantly elevated levels in the serum and plasma from schizophrenia patients (Table 1). In addition, chromogranin A was also found at significantly elevated levels.

Glucose levels were unchanged in schizophrenia patients, except for cohort 3, which showed a slight elevation (Table 1). Therefore, the observed changes in insulin-related molecules occurred against a background of relatively normal glucose levels, suggesting that at least some patients show signs of insulin resistance. Another factor that should be considered is the lack of gender balance in some cohorts. However, covariate analyses showed that this factor had no influence on analyte levels (data not shown). This shows the reproducibility of the findings irrespective of confounding factors such as glycemic status and gender. In contrast, no significant differences were found regarding insulin-related molecules in bipolar