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SCIENTIFIC CORRESPONDENCE

Brain potential amplitude varies as a function of Borna disease virus-specific immune complexes in obsessive–compulsive disorder

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SIR—Borna disease virus (BDV), a unique virus with a nonsegmented, single-strand RNA-genome of negative polarity,[1] causes behavioral disturbances in animals.[2] The discovery of BDV-specific antibodies and viral components (proteins, RNA) in peripheral blood mononuclear cells (PBMCs)[3] in humans, in particular in psychiatric patients,[4] as well as the isolation of infectious virus from PBMCs[5] and brain[6] of such patients has suggested a role of BDV in the etiology of depression[4] and/or obsessive–compulsive disorder (OCD).[5,7] How BDV may impact behavioral or neurophysiological disturbances in OCD, however, is unknown. Controversial findings[6] on the prevalence of BDV appear to result from different infection markers and detection methods, but BDV-specific circulating immune complexes (CICs) are indicating a high prevalence of BDV in these disorders.[7]

In this pilot study, we provide evidence that BDV infection in OCD is associated with changes in neural correlates of cerebral information processing. We used a visual Go/Nogo-reaction time experiment[8] to investigate attentional processes by means of event-related brain potentials (ERPs) in OCD patients and controls matched for age, sex and educational years ($n=12$, each). All the OCD patients fulfilled the DSM-IV criteria, but differed significantly regarding the amount of BDV-specific CICs in plasma. CICs were detected by an enzyme immune assay (EIA) using immobilized BDV-specific anti-p40/p24 monoclonal antibodies.[7] A median split (six patients, each) led to group L with low levels of CICs (85.5 ± 47 as extinction $\times 1000$ at 405 nm) and a high level group H (504.7 ± 316). Severity of OCD symptoms (Y-BOCS, L: 21.8 ± 7, H: 25 ± 3), secondary depression (HAMD-score, 21-items, L: 14.8 ± 10, H: 15.8 ± 5), age (L: 33.7 ± 12, H: 34.8 ± 8 years), additional medication and educational years (L: 14 ± 3, H: 13.7 ± 1 years) did not differ between groups.

The experimental procedure called for a button press to one kind of stimuli (Go), while subjects had to withhold a response for the other kind (NoGo). ERPs were obtained using standard procedures.[8] Given the importance of attention-related fronto-striatal system hyperactivity in OCD,[9] we focused on the N1, a negative ERP component with temporoparietal maximum, and a peak latency of about 170 ms in this study. We found (Figure 1a) a dramatic increase of the N1 amplitude (average across Go and NoGo stimuli) and an elevated amplitude of the frontal P2/N2 complex (not shown) for group H patients, compared to both, group L and control subjects, but no significant differences for N1 peak latency between these three groups. In addition, no differences in reaction times and hit rates were observed between the high and low groups (H: 515 ± 34, L: 560 ± 32 ms; H: 98.7 ± 1, L: 98.6 ± 2%) as well as

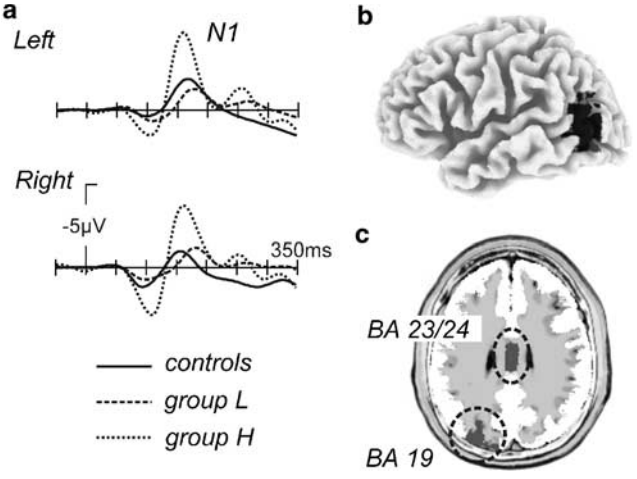

Figure 1 (a) Grand-average ERPs from left and right temporoparietal sites (P7/P8) showing a marked increase of N1 amplitude for group H. Mean amplitude (160–180 ms) at this electrode pair showed an overall group difference ($F(2,21)=6.98$; $P<0.005$) with *post hoc* tests (Scheffé) indicating differences between group H and controls ($P<0.01$), group H and group L ($P<0.01$), but no difference between group L and controls. (b) Source analysis (LORETA) for the grand average showed a prominent left temporoparietal source at 152 ms for group H subjects corresponding to Brodmann areas 19/37/39. Voxels in the region marked in black showed activity higher than 0.01 μA/mm^2. (c) A statistical comparison of the individual source solutions (LORETA, time window 140–180 ms) of group H and control subjects revealed group differences in medial frontal and lateral temporo-occipital regions. The darker zones (encircled) represent those voxels for which *t*-values exceeded the threshold of significance (corrected for multiple comparisons).

between OCD patients and controls (RT: 537±39 *vs* 528±50 ms; HR: 98.6±1 *vs* 98.2±2%), respectively. Neural generators of the N1 were estimated with the LORETA method, indicating a major source in the left temporoparietal region (Brodmann areas (BA) 19/37/39, Figure 1b) and a weaker mirror image source on the right. Comparing individual source solutions statistically (voxel-wise), group H and the control group differed in the medial frontal (BA 23/24) and lateral temporo-occipital (BA 19) cortex (Figure 1c).

This is the first demonstration that BDV activity (amount of BDV-CICs) is associated with disease-relevant and attention-related cognitive changes (increased N1) in humans, in particular in secondary visual areas and the anterior cingulate gyrus. The increased N1 amplitude in group H patients may be explained by defective thalamic filter mechanisms, given a proposed modulation by thalamic input to the cortex.[10] Indeed, functional neuroimaging studies[9] strongly suggest that OCD involves hyperactivity of striato-thalamo-cortical networks. The present findings are consistent with such a hyperactivity and suggest that this may be modulated by BDV infection possibly through interference of viral components with neurotransmitters (eg, glutamate and aspartate).[4] Future studies should validate these findings and further investigate possible mechanisms of this neurotropic virus in relation to altered cortical activity in psychiatric disorders.

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Variation at the *DRD4* promoter modulates extraversion in Caucasians

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SIR—Dopamine receptor genes have attracted considerable interest on account of their involvement in cortical processing, their evolutionary dynamics, and in view of growing prospects for the visualization of dopamine-related changes in brain activity. Variants of the dopamine D4 receptor gene (*DRD4*), in particular, have been studied extensively, following reports of their suspected role in Novelty Seeking, and related personality dimensions.[1] However, the issue remains unresolved owing to several potential confounders. While early investigations examined a 48 bp VNTR in exon III, conflicting findings with regard to personality traits have raised concerns that the grouping of alleles at this site may overstate what are only minor functional differences.[2] Others have pointed out a number of exon III alleles of unknown function nested in length variants.[3] More recently, the focus of attention has thus shifted towards *DRD4* markers located in the gene's promoter region, on account of their relevance to gene expression.[4,5] In particular, two variants are currently being regarded as modulators of *DRD4* expression; namely, a 120 bp promoter length polymorphism (refSNP-ID rs4646984), and a −521T>C marker (refSNP-ID rs1800955) mapped to the gene's core promoter,[6] which was also implicated in the modulation of Extraversion in African Americans.[7] The present investigation was designed to test these polymorphisms as possible genetic determinants of personality traits in a larger population of healthy subjects.

A total of 104 Caucasian volunteers (52 males, mean age = 29.1±7.5 years, and 52 females, mean age = 28.1±7.6 years) were recruited from Regensburg University, or the Regensburg area, and completed the German version of the NEO-FFI questionnaire. The *DRD4* promoter markers were assessed using PCR-based protocols previously described,[4,5] and were confirmed to be in Hardy–Weinberg equilibrium. Allele and genotype frequencies were in close agreement with results from previous studies in Caucasians ($f_S = 0.21$ for allele grouping, see below; $f_T = 0.54$). For the promoter repeat, the lesser allele (S) was considered dominant to maximize balance in genotype ratios. For the −521T>C marker, we considered T the dominant allele to match the previous study.[7] One-way analyses of variance (ANOVA) identified carriers of the promoter 120 bp single repeat allele (short, S, as opposed to long, L, for 2 repeats) as exhibiting higher mean

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