6409T > C *D18S40* haplotype was also associated with schizophrenia ($P = 0.012$), while the 6409T > C-*D18S40*–($P = 0.274$) and *D18S852–D18S40* ($P = 0.138$) were not. The *C18orf1* protein is predicted to have a putative type Ib transmembrane domain, a low-density lipoprotein receptor class A domain, potential binding sites for src homology 3 and tryptophan tryptophan–domains. It may therefore function by interacting with signaling molecules.[5]

From the data presented here, *C18orf1* as well as *GNAL* and *IMPA2* on the short arm of chromosome 18 (within a 1.5 Mb region, Table 1) show association with schizophrenia or functional psychoses.[1,6] Recent examples showing fine mapping of complex diseases have demonstrated the significance of clustered positive markers around causal variants frequently interspersed with non significant markers.[11] In this context, the present findings support the idea that the proximal area of 18p is a schizophrenia susceptibility locus, and indicate that the genomic region surrounding the *C18orf1* gene warrants further scrutiny.

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Hypothalamic–pituitary–adrenal (HPA) system activity in depression and infection with Borna disease virus and *Chlamydia pneumoniae*

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SIR – The pathophysiology of severe depression may be associated with mutual immune and hypothalamic–pituitary–adrenal (HPA) system activation,[1,2] by which infection-induced immune response is triggering the HPA system, thereby changing behavior,[3] and stress hormones, in turn, the immune system.[4] In this context, we investigated infections with two independent agents (Borna disease virus (BDV) and *Chlamydia pneumoniae* (CP)), one of which already under debate to specifically contribute to depression.[5–8] Our study provides the first clinical evidence that in depressed patients, infection with Bornavirus is associated with activation of the HPA system.

The study enrolled 48 patients with a major depressive episode (DSM-IV), giving informed consent and presenting with at least 18 points in the Hamilton Depression Scale (HAMD) after a 6-day wash-out, who were kept off psychotropic medication for 1 week (except lorazepam and zolpidem) and subsequently treated with 150 mg amitriptyline or 40 mg paroxetine for weeks 1–4. Excluded were patients with schizophrenia, bipolar or current substance-related disorders. Saliva cortisol was measured daily at 8.00, 16.00 and 22.00 h during weeks −1 to 4, and mean daily concentrations were calculated each week. Citrated blood was drawn weekly for 6 weeks. IgG, IgM and IgA antibodies to CP were analyzed twice (weeks −1 and 4) using a commercially available assay. BDV structural proteins p40 and p24 and specific circulating immune complexes (CICs), together indicating antigenemia as a result of viral replication, were determined by enzyme immune assays (EIAs) using specific monoclonal antibodies.[5,8] BDV antigen-positive scoring requested moderate or high reactivity in the BDV-CIC and/or plasma antigen EIA. Nonreactivity in either assay was considered BDV negative. Laboratories (endocrinology, microbiology) were mutually kept blind as to their results. Analysis of variance with repeated measures (ANOVA-rm) and *t*-tests were used to compare HPA system activity between subgroup of patients.

A total of 16 patients were BDV antigen positive at one or more time points, while 17 did not show positive BDV antigen in any of 6-weekly blood samples. In all, 15 subjects were excluded because BDV antigen results did not allow clear stratification. BDV antigen-positive and -negative subgroups did not differ with respect to age (54 ± 12 *vs* 52 ± 13 years), pre-treatment, severity (HAMD: 24 ± 4 *vs* 24 ± 5) or subtype of depression, antidepressive treatment (seven paroxetine/nine amitriptyline *vs* nine paroxetine/eight amitriptyline) or use of lorazepam during the study or HAMD score at day 28 (15 ± 9 *vs* 11 ± 6). A higher proportion of women (13/22) than men (3/11) was BDV antigen positive.

Using ANOVA-rm, we found increased baseline cortisol in the BDV antigen positive compared to the negative group (effect of group: $F_{1,60} = 5.79$, $P < 0.03$; effect of time: $F_{2,60} = 128.24$, $P < 0.0001$; 8.00 h:

28.1±12.8 *vs* 21.6±7.3, $P<0.09$; 16.00 h: 11.4±6.2 *vs* 6.3±2.7; 22.00 h: 6.3±3.5 *vs* 3.5±1.6 nmol/l, both $P<0.01$). These results were not influenced by gender. Based on a normative database, morning saliva concentrations above 25 nmol/l are indicative of HPA system activation. Evidence for increased cortisol concentrations in the BDV-positive group is further supported by declining values during treatment exclusively within the BDV-positive group (time of group interaction: 8.00 h: $F_{4,120}=2.03$, $P<0.1$; 16.00 h: $F_{4,124}=3.85$, 22.00 h: $F_{4,120}=3.69$, both $P<0.01$). Patients without clear BDV stratification had intermediate cortisol concentrations. Their inclusion did not change the above effects. Regarding CP, 10 patients were IgG positive, while 36 patients were IgG negative. These groups did not differ with respect to age, gender, severity of depression or mean saliva cortisol concentrations. No statistical analysis was possible for CP IgM- ($n=1$) and IgA-positive patients ($n=1$).

BDV infection was studied with respect to its potential role in depression, suggested by mRNA/antigen in such patients' blood and cerebrospinal fluid, virus isolates from white blood cells,[5] and antigenemia correlating with severity.[7,8] Further, a relation, whatsoever, of depressed patients' HPA system activity to impaired immune functions, thereby promoting BDV replication, was hypothesized.[6] Our findings add evidence to this assumption, showing high pretreatment cortisol concentrations in such patients together with signs of replication of a neurotropic virus, causing CNS cytokine expression (9) and behavioral disorders in animals.[7] However, this does not provide sufficient evidence for any causal relation. Clinically, no significant difference between BDV antigen-positive and -negative patients could be detected. Our data still leave several plausible modes of interaction between the HPA system and BDV replication: hippocampal BDV infection or BDV-induced cytokine response may lead to HPA feedback dysregulation or increased HPA activity may lead to impaired immune function and BDV replication. BDV activation possibly preceding HPA system activation would be in accordance with changes of cytokine and endocrine signaling in the context of inflammation.[1]

CP is a Gram-negative bacterium being involved in various disorders, including coronary heart disease (CHD). CHD is related to depression, although the causal relation between both conditions is not completely understood.[10] This study showed that HPA system activation is unrelated to CP. In contrast to active BDV infection, CP sero-positive patients did not show increased baseline HPA system activity. Regarding immunity to CP, only one patient was IgM positive, but the vast majority of patients did not suffer from active or persistent CP infection.

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