Neurostructural correlates of NCAN, a genome-wide significant risk gene for psychiatric disorders

Harald Kugel[1], Udo Dannlowski[2,3], Dominik Grotegerd[2], Ronny Redlich[2], Janina Suchy[2], Nils Opel[2], Thomas Suslow[2,4], Carsten Konrad[3], Patricia Ohrmann[2], Jochen Bauer[2], Tilo Kircher[3], Axel Krug[3], Andreas Jansen[3], Bernhard T Baune[5], Walter Heindel[1], Katharina Domschke[6], Volker Arolt[2], Christa Hohoff[2], Marcella Rietschel[7], and Stephanie H Witt[7]

[1]Department of Clinical Radiology, University of Münster, Muenster, NRW, Germany, [2]Department of Psychiatry, University of Münster, Muenster, NRW, Germany, [3]Department of Psychiatry, University of Marburg, Marburg, HE, Germany, [4]Department of Psychosomatic Medicine and Psychotherapy, University of Leipzig, Leipzig, SN, Germany, [5]Discipline of Psychiatry, University of Adelaide School of Medicine, Adelaide, SA, Australia, [6]Department of Psychiatry, University of Würzburg, Würzburg, BY, Germany, [7]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, BW, Germany

Purpose: Bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ) are highly heritable. Genome-wide association studies have reported an association between *NCAN* rs1064395 genotype and BD, MDD, and SCZ, suggesting that this is a vulnerability factor for these disorders [1-4]. However, the neurobiological underpinnings of these associations are poorly understood. *NCAN* is implicated in neuronal plasticity and expressed in subcortical brain areas, such as the amygdala and hippocampus [1,5-6], which are critically involved in dysfunctional emotion processing and -regulation across diagnostic boundaries [7-14]. We hypothesized that the *NCAN* risk variant containing the A-allele is associated with reduced gray matter volumes in these areas both in healthy subjects and in subjects with MDD.

Methods: Gray matter structure was assessed by voxel-based morphometry on structural MRI-data in two independent German cohorts (healthy subjects, n = 512, 289 female, 33.3 ± 11.6 y; study repeated with inpatients with MDD and a current depressive episode, n = 171, 105 female, 38.6 ± 11.7 y). All participants were genotyped for *NCAN* rs1064395. MR images were acquired on a 3 T-MR scanner (Gyroscan Intera 3T, Philips, Best, NL) with a 3D fast gradient echo sequence (TFE), TR/TE/FA 7.4 ms/3.4 ms/9°, inversion prepulse every 816 ms, acquired over a FoV of 256 mm (FH, frequency encoding) x 204 mm (AP, phase encoding) x 160 mm (RL, 2nd phase encoding) with cubic voxels of 1 mm edge length, reconstructed to 0.5 mm. Hippocampal and amygdala region-of-interest analyses were performed within each cohort, using the VBM8-toolbox [15] including DARTEL normalization. Group statistics were calculated using SPM8. Additionally, whole-brain data from the combined sample were analyzed to detect possibly affected brain areas for which no a-priory hypothesis exists.

Results: Risk (A)-allele carriers (genotypes AA, AG) showed reduced amygdala and hippocampal gray matter volumes, compared to carriers of the G-allele (genotype GG), in both cohorts with a remarkable spatial overlap (Fig. 1). In the combined sample, genotype effects observed for the amygdala and hippocampus survived correction for entire brain volume. Further effects were also observed in the left orbitofrontal cortex and the cerebellum/fusiform gyrus (Fig. 2).

Discussion: *NCAN* genotype is associated with limbic gray matter alterations in areas implicated in emotion processing and regulation in healthy subjects as well as in depressed subjects. Since patients with bipolar disorder, major depressive disorder, and schizophrenia show functional and structural abnormalities in these areas, the present data suggest that the increased susceptibility of risk allele carriers for disorders might be moderated by neurostructural deficits in the amygdala, hippocampus, and prefrontal areas, leading in turn to dysfunctional emotion processing.

Conclusion: The genetic variant may indicate a susceptibility to abnormal brain structure in areas implicated in emotion processing and regulation. While this is independent of psychiatric disease, the influence on brain structure may form an additional susceptibility to disorders seen in BD, MDD, and SCZ.

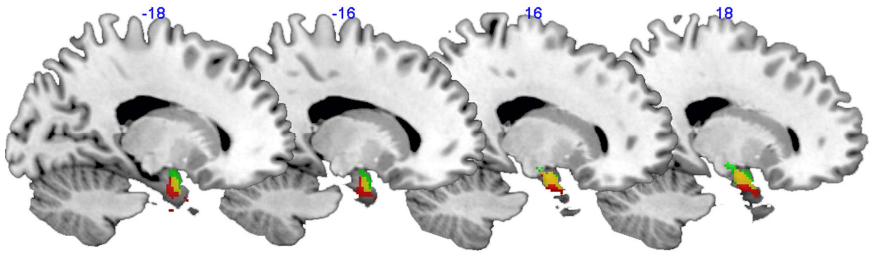

Fig. 1. Sagittal views of left and right amygdala and the hippocampus region depicting the effect of *NCAN* rs1064395 genotype on gray matter volumes in the two samples, corrected for gender and age, rendered on a brain template in MNI space. Red: Results from healthy subjects showing N=389 GG homozygotes > N=123 A-carriers (AA and AG), threshold p<0.01, cluster threshold k=160 voxels, resulting cluster-corrected threshold p<0.05. Green: Results from MDD patients showing N=124 GG > N=47 A-carriers, same statistical threshold. Yellow: Overlap between the clusters of each sample. Blue values, MNI x-coordinate.

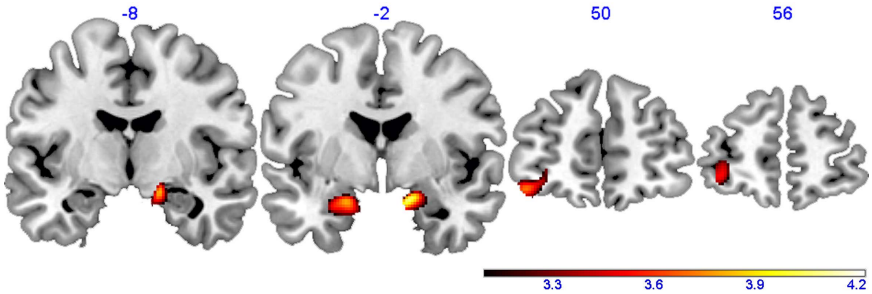

Fig. 2. Coronal views (blue values, MNI y-coordinate) of the hippocampus head, amygdala, and orbitofrontal cortex depicting the effect of *NCAN* rs1064395 genotype (GG > A-carrier) on gray matter volumes in the combined sample (N=683), corrected for gender, age, and subsample. Color bar, t-value.

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