Influence of genetic variations in \textit{IL1B} on brain region volumes in bipolar patients and controls

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**ABSTRACT**

Involvement of the immune system has been implicated in the etiology and pathophysiology of mood disorders, including bipolar disorder. Neuroimaging studies have reported structural brain pathology in bipolar disorder patients, and both levels of and genetic variants in cytokines have been associated with altered volumes of brain regions. The aim of this study was to investigate associations between single nucleotide polymorphisms in the gene coding for the pro-inflammatory cytokine interleukin-1 beta (\textit{IL1B}) and whole brain grey matter volume, as well as volumes of several brain regions shown to be of importance in mood disorders. Structural magnetic resonance imaging and vertex-based morphometry were used to obtain volume of different brain regions in subjects with bipolar disorder (n=188) and healthy controls (n=54). Four \textit{IL1B} polymorphisms were genotyped: rs1143623, rs1143627, and rs16944 in the promoter region together with the synonymous variant rs1143634 in the \textit{IL1B} gene. The genotype distribution did not differ between bipolar subjects and controls. The T allele at rs16944 and the C allele at rs1143627 were associated with increased volumes of the putamen of the left hemisphere in patients and controls, which lends support to the role of this immune system mediator for brain structure.

1. Introduction

The immune system has been demonstrated to play an important role in brain development and plasticity (Boulanger, 2009), and has also been implicated in the pathophysiology of mood disorders such as bipolar disorder (Goldstein et al., 2009; Maes and Carvalho, 2018). Bipolar disorder is a lifelong psychiatric disease characterized by recurrent episodes of mania or hypomania and episodes of depressed mood interspaced with periods of euthymia. Studies have shown cognitive impairment associated with the disorder (Abé et al., 2018; Pålsson et al., 2013; Rolstad et al., 2016; Solé et al., 2017; Sparding et al., 2015) along with structural and neurophysiological changes (Abé et al., 2019, 2016; Berk et al., 2011; Hibar et al., 2018). Cognitive performance has been associated with levels of neuroinflammatory biomarkers in the cerebrospinal fluid (CSF) in patients with bipolar disorder but not in healthy controls (Rolstad et al., 2015), suggesting that inflammation may be part of the underlying causes for cognitive decline in individuals with bipolar disorder. In addition to frequent psychiatric comorbidity (Kessler et al., 2005), individuals with bipolar disorder are reported to have higher rates of medical conditions with a serious inflammatory component, including cardiovascular diseases, diabetes, and rheumatoid arthritis (Cremaschi et al., 2017; Goldstein et al., 2009). The pro-inflammatory cytokine interleukin-1 beta (IL-1beta) has been implicated in the pathophysiology of all of these diseases as well as in mood disorders (Maes and Carvalho, 2018). IL-1beta is involved in acute and chronic neurodegeneration (Simi et al., 2007) and in embryonic development of the central nervous system (Ratnayake et al., 2013), where it promotes proliferation and production of cytokines and trophic factors. It has been shown to be of relevance for brain plasticity in animal studies, e.g. in axonal plasticity after spinal cord injury (Boato et al., 2013) as well as hippocampal synaptic plasticity (Erion et al., 2014). A meta-analysis of 30 clinical studies revealed significantly higher peripheral IL-1beta levels in patients with bipolar disorder compared with controls (Modabbernia et al., 2013). With respect to central expression, levels of IL-1beta were elevated in the cerebrospinal fluid of bipolar patients compared with controls – a trend that was even more pronounced depending on the manifestation of manic/hypomanic episodes during the year prior to sampling (Söderlund et al., 2010).

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Numerous studies have attempted to identify anatomical networks and brain systems that underlie emotional behaviour and mood disorders, and animal studies together with human neuroimaging studies have implicated several structures to be of importance (Price and Drevets, 2010); these include, amongst others, the amygdala, hippocampus, caudate nucleus, globus pallidus, nucleus accumbens, putamen, and thalamus.

The polymorphisms included in this study have been implicated in the clinical expression of several diseases suggesting functionality of the SNPs; rs1143634 has been associated with cancer (Rosero et al., 2016), rs1143623 with triglyceride levels and interleukin-6 (IL-6) metabolism (Delgado-Lista et al., 2011), and both rs1143634 and rs1143623 with decreased risk, clinical features, and better overall survival of colorectal cancer (Qian et al., 2018). Furthermore, candidate gene studies investigating the role of IL1B variations in psychiatric morbidity have found associations with several psychiatric conditions. Haplotype analysis of the SNPs rs16944 and rs1143627 found variants of these polymorphisms to be significantly different between patients with major recurrent depression and controls (Borkowska et al., 2011), and rs16944 has been implicated in both schizophrenia and bipolar disorder (Papiol et al., 2004), as well as with whole brain grey matter deficits in bipolar patients (Papiol et al., 2008).

The aim of this study was to investigate whether the variation in the IL1B gene and its promoter was associated with whole brain grey matter volume and volume of different brain areas of importance for mood disorders. For this purpose, we analysed four SNPs in IL1B; rs1143623, rs1143627 and rs16944 that lie upstream of the IL1B gene together with rs1143634, which is a synonymous variant in the gene, in a sample of 188 patients with bipolar disorder and 54 healthy controls.

2. Methods

2.1. Participants

Patients were recruited from the St. Göran Bipolar Project, which provides assessment, treatment, and follow-up of patients with bipolar disorder within the Northern Stockholm Mental Health Service and also serves as a basis for research into bipolar disorder. The methodology has previously been described in detail (Ekman et al., 2010). Patients were diagnosed for bipolar disorder according to the DSM-IV using a Swedish version of the structured interview instrument Affective Disorder Evaluation (ADE). The interviews were conducted by board-certified psychiatrists working at the tertiary bipolar outpatient unit, or residents in psychiatry completing their training at this unit. The assessments were based on the patients’ self-reports and the clinicians’ evaluation, and, when needed, supplemented with information from medical records and interviews with next of kin. A total of 188 patients with bipolar disorder and 54 controls were included in this study. Demographics and clinical characteristics of the study population are shown in Table 1. Demographics and clinical characteristics of the study population.

| Demographic/clinical characteristics | Controls | Bipolar Disorder |
|--------------------------------------|----------|------------------|
| Number                               | 54       | 188              |
| Age mean (min-max)*                  | 40 (21-74)| 38 (18-73)       |
| Sex (male/female)*                   | 22/32    | 74/114           |
| Diagnosis (BPD-I/II/NOS)**           | 100/65/23| 106/65/23        |
| No. manic episodes, mean (min-max)   | 1 (0-25) | 1 (0-25)         |
| No. depression episodes, mean (min-max)| 5 (0-80)| 5 (0-80)         |
| Lithium treatment, n (%)             | 111 (59%)| 111 (59%)        |
| Antidepressant treatment, n (%)      | 89 (47%) | 89 (47%)         |
| Antipsychotic treatment, n (%)       | 49 (26%) | 49 (26%)         |
| Anticonvulsant treatment, n (%)      | 71 (38%) | 71 (38%)         |

* Independence samples t-test showed no statistically significant difference in the distribution of age or sex between patients and controls.
** BPD-I= bipolar disorder type I, BPD-II=bipolar disorder type II, NOS=Not otherwise specified.

2.2. Ethics

All participating patients and control subjects gave oral and in written consent to participate in the study, and the project was approved by the Stockholm Regional Ethical Review Board (Dnr: 2005/554-31/3, 2009/1221-32).

2.3. Acquisition and preprocessing of MRI data

Magnetic resonance imaging (MRI) scans were acquired at the MR Research Centre, Karolinska University Hospital, Stockholm. A more detailed description of the methodology has been reported previously (Liberg et al., 2014). A General Electric Signa HDxt 1.5 T scanner (Milwaukee, WI, USA) was used to acquire two T1-weighted anatomical images in each subject and a consultant in neuroradiology did a radiological assessment of the anatomical scans of each individual to rule out gross signs of pathology. FMRIB’s Integrated Registration and Segmentation Tool (FIRST, v 1.2) was used for automatic segmentation of the following subcortical brain structures in both hemispheres: amygdala, caudate nucleus, globus pallidus, hippocampus, nucleus accumbens, putamen, and thalamus. Intracranial volume was calculated with FMRIB’s Structural Image Evaluation using Normalisation of Atrophy for cross-sectional measurement (SIENAX). Each brain was segmented into three tissue types: grey matter, white matter, and cerebrospinal fluid. Intracranial volume was defined as the sum of those tissue volumes. A scaling factor for each participant was calculated using SIENAX. This factor was derived from the difference in size of each individual brain in relation to the Montreal Neurological Institute (MNI) 152 standard brain and used to normalize all volumetric measures in each subject.

2.4. Genotyping

DNA was extracted from blood samples from patients and controls. Genotyping of four SNPs in IL1B (rs1143623, rs1143627, rs1143634 and rs16944) was conducted using the Kompetitive Allele Specific (KAS-Par®) PCR SNP genotyping system (LGC Genomics, Hoddesdon, UK).

2.5. Statistical analysis

All statistical analyses were performed using SPSS Statistic version 22 (IBM Corp.). Independent samples t-test was used to evaluate any difference in age between patients and controls. Chi-square test for independence was used to analyse the distribution of genotypes as well as the distribution of sex between patients and controls. Analysis of covariance (ANCOVA) was performed to analyse the effect of genotype on whole brain grey matter and brain region volumes, with age, sex, patient-control, type of bipolar disorder (type I, type II, and not otherwise specified (NOS)), lithium treatment, number of manic episodes, and filter (as the calibration filter of the MRI scanner was changed during the study) as covariates.

Linkage disequilibrium (LD) was analysed using the pairwise LD measure D’ and a LD plot showing D’ and r2 was generated using Haploview software (Barrett et al., 2005). Fig. 1 shows the LD plot of the four SNPs in IL1B (rs1143623, rs1143627, rs1143634 and rs16944). To correct for multiple testing, the Bonferroni method was applied; the analyses of four SNPs and the left and right hemisphere of seven brain regions as well as whole brain grey matter and brain region volumes, with age, sex, patient-control, type of bipolar disorder (type I, type II, and not otherwise specified (NOS)), lithium treatment, number of manic episodes, and filter (as the calibration filter of the MRI scanner was changed during the study) as covariates.

Chi-square for independence analysis revealed that IL1B genotype was not associated with diagnosis for any of the SNPs, see Table 2.
The LD plot of the four SNPs in \textit{IL1B} (rs1143623, rs1143627, rs1143634 and rs16944) show very high linkage between some of the investigated SNPs, see Fig. 1.

The results from the ANCOVA analysis to explore the effect of genotype on whole brain grey matter and volumes of globus pallidus, putamen and thalamus are shown in Table 3. We found nominal associations for several of the investigated polymorphisms with volume of globus pallidus, putamen and thalamus in patients and controls. However, only the associations between the SNPs rs1143627 and rs16944 and volume in the putamen of the left hemisphere survived Bonferroni correction for multiple testing.

No associations were seen between genotype in any of the investigated polymorphisms and volume of amygdala, caudate nucleus, hippocampus or nucleus accumbens.

4. Discussion

In this study, variations in the \textit{IL1B} gene were investigated with respect to brain region volumes in controls and bipolar patients. No differences between the two cohorts were detected but the SNPs rs16944 and the C allele at rs1143627 were associated with increased volumes in all investigated areas except the globus pallidus in the left hemisphere and the hippocampus. Only the associations in the left hemisphere putamen hold for multiple correction. The putamen is a substructure of the basal ganglia and forms, together with the caudate nucleus, the dorsal striatum. The main function of the basal ganglia is the selection and implementation of purposeful actions in response to external and internal cues (Simonyan, 2019). More specifically, the putamen has been shown to be activated most strongly during anticipation of reward, whereas the caudate nucleus is activated most strongly during the receipt thereof (Liu et al., 2011). This function of the putamen is likely related to anhedonia, and smaller volume of the putamen has been associated with anhedonia symptoms (Sachs-Ericsson et al., 2018). A MRI study compared functional connectivity of different striatal sub-regions in bipolar disorder patients during an episode of depression or (hypo)mania, respectively, as well as healthy controls (Altinay et al., 2016). In addition to widespread functional connectivity abnormalities between striatal subregions and frontal cortices, limbic regions, and midbrain structures common to patients with bipolar disorder, they found that patients displaying depressive symptoms exhibited increased connectivity of the putamen with areas involved in cognitive and autonomic responses to emotional stimuli (Altinay et al., 2016).

Interestingly, inflammation with respect to raised plasma levels of C-reactive protein has been associated with decreased dorsal striatum-ventromedial prefrontal cortex connectivity leading to the assumption that anti-inflammatory treatment may be indicated in the depressed patients to improve motivational and motor deficits since the findings also were linked to anhedonia, motor speed and psychomotor function. Also increased plasma levels of Il-beta predicted decreased connectivity (Felger et al., 2016). These findings support our notion that genetic variation in \textit{IL1B} may be of importance for brain function and the etiology of mood disorders.

Analysis of linkage disequilibrium revealed that three of the investigated SNPs are in nearly complete linkage: rs1143627, rs16944, and rs1143623. All three are in the promoter region of the \textit{IL1B} gene and may affect binding of transcription factors, but due to the high degree of linkage it is not possible to conclude which of these SNPs play a role in the observed phenotype on a molecular genetic level. In \textit{in vitro} studies have investigated the functional implications of rs16944 and rs1143627; a haplotypic combination of these variants has been associated with increased binding of transcription factors to the \textit{IL1B} promoter in \textit{in vitro} (Chen et al., 2006), and the C allele at rs1143627 has been found to inhibit protein complex formation at this site, indicating that some transcription factors may be unable to bind and form the transcription initiation complex (El-Onmar et al., 2000). However, the latter study found no differences in binding activity for the T allele at rs16944. The T allele at rs16944 has also been associated with later onset of depression (Hwang et al., 2009) and with lower severity of depressive
### Table 3
Association between polymorphisms in *IL1B* and whole brain grey matter volume (in mm³), as well as volume of globus pallidus, putamen and thalamus, both in the left hemisphere (LH) and the right hemisphere (RH) in means (SD).

| Genotype | n  | Grey matter (LH) | RH (LH) | Globus pallidus (LH) | RH (LH) | Putamen (LH) | RH (LH) | Thalamus (LH) | RH (LH) | Grey matter (RH) | RH (RH) | Globus pallidus (RH) | RH (RH) | Putamen (RH) | RH (RH) | Thalamus (RH) | RH (RH) |
|----------|----|------------------|---------|----------------------|---------|--------------|---------|---------------|---------|------------------|---------|------------------|---------|--------------|---------|---------------|---------|---------------|---------|
| rs1143623|    |                  |         |                      |         |              |         |               |         |                  |         |                  |         |              |         |               |         |              |
| CC       | 25 | 817134 (64983)   | 0,016   | 2454 (230)           | 0,1     | 2452 (193)   | 0,019   | 6983 (719)    | 0,004  | 6662 (685)      | 0,033  | 11418 (890)     | 0,029  | 11120 (842)   | 0,024  |
| CG       | 94 | 790846 (70620)   |          | 2354 (287)           |         | 2310 (324)   |         | 6448 (998)    |         | 6229 (917)      |         | 10960 (1085)    |         | 10672 (1083)  |         |
| GG       | 116| 787393 (74188)   |          | 2325 (243)           |         | 2286 (260)   |         | 6376 (888)    |         | 6228 (847)      |         | 10957 (1134)    |         | 10647 (1102)  |         |
| rs1143627|    |                  |         |                      |         |              |         |               |         |                  |         |                  |         |              |         |               |         |              |
| CC       | 32 | 820331 (68296)   | 0,005   | 2442 (221)           | 0,1     | 2441 (177)   | 0,017   | 7018 (660)    | 0,00079* | 6697 (648)      | 0,008  | 11321 (915)     | 0,028  | 11056 (875)   | 0,015  |
| TC       | 108| 783729 (75755)   |          | 2335 (204)           |         | 2286 (337)   |         | 6347 (1034)   |         | 6161 (958)      |         | 10838 (1205)    |         | 10534 (1200)  |         |
| TT       | 95 | 790892 (68117)   |          | 2339 (217)           |         | 2300 (236)   |         | 6426 (824)    |         | 6262 (785)      |         | 11071 (1014)    |         | 10769 (970)   |         |
| rs1143634|    |                  |         |                      |         |              |         |               |         |                  |         |                  |         |              |         |               |         |              |
| CC       | 122| 794702 (71583)   | 0,3     | 2344 (255)           | 0,4     | 2322 (273)   | 0,1     | 6511 (814)    | 0,05   | 6318 (750)      | 0,033  | 11014 (1061)    | 0,7    | 10729 (1019)  | 0,9    |
| TC       | 101| 790672 (74046)   |          | 2368 (272)           |         | 2324 (294)   |         | 6491 (1041)   |         | 6293 (960)      |         | 11007 (1138)    |         | 10679 (1133)  |         |
| TT       | 11 | 768594 (71641)   |          | 2246 (230)           |         | 2102 (266)   |         | 5838 (923)    |         | 5654 (1012)     |         | 10924 (1319)    |         | 10675 (1370)  |         |
| rs16944  |    |                  |         |                      |         |              |         |               |         |                  |         |                  |         |              |         |               |         |              |
| CC       | 95 | 790376 (67787)   | 0,005   | 2337 (217)           | 0,1     | 2302 (235)   | 0,022   | 6415 (820)    | 0,00076* | 6251 (778)      | 0,007  | 11050 (1030)    | 0,1    | 10755 (977)   | 0,024  |
| TC       | 106| 782328 (75957)   |          | 2336 (306)           |         | 2290 (340)   |         | 6338 (1040)   |         | 6151 (964)      |         | 10855 (1208)    |         | 10535 (1206)  |         |
| TT       | 32 | 820331 (68296)   |          | 2442 (221)           |         | 2441 (177)   |         | 7018 (660)    |         | 6697 (648)      |         | 11321 (915)     |         | 11056 (875)   |         |

SD: standard deviation
p: p-value. Bonferroni adjusted significant p-values are indicated by an asterisk.
have been negatively associated with whole brain grey matter volume, as well as with an upregulated mRNA expression. Two independent cohorts were studied consisting of both controls and patients diagnosed with schizophrenia as well as post-mortem material.

In contrast, in a study in bipolar patients the rs16944 T allele was associated with lower grey matter volumes (Papiol et al., 2008). However, the sample size in that study was low (n=20), and the reported results would not have survived correction for multiple testing. Furthermore, the grey matter deficits reported by Papiol et al. were mainly focused in the prefrontal cortex, an area that was not investigated in our study. The T allele at rs16944 has also been associated with frontal grey matter deficits in patients with schizophrenia but not in healthy controls (Mostaid et al., 2019). The latter study furthermore found no association between schizophrenia and the rs16944 polymorphism in IL1B. A study in patients with major depressive disorder investigating this SNP also found no difference in the distribution of the genotype in rs16944 between patients and controls (Yu et al., 2003). This, together with our results showing no association between this SNP and bipolar disorder, may suggest that the genetic variation in IL1B might not have a pathogenic effect per se. Nevertheless, it shows clear associations with differences in brain volume, and may lead to psychiatric morbidity when combined with other risk-factors.

A study in elderly individuals with depression reported no effect of rs16944 on geriatric depression susceptibility or severity. Nevertheless, they found that patients who were T/T homozygotes showed a significantly later depression age of onset (Hwang et al., 2009), suggesting that the C allele at this polymorphism in IL1B may enhance molecular mechanisms leading to an earlier manifestation among individuals already vulnerable to depression, but not cause the disorder or affect its severity per se. However, lower severity of depressive symptoms and higher treatment response to antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) have been associated with the T allele of this SNP, although no difference was detected in the genotype distribution of the rs16944 polymorphism between depressed patients and controls (Yu et al., 2003). Another study also found that major depressive disorder patients that carried the rs16944 T allele had significantly faster and more pronounced response to an SSRI, but not to a tricyclic antidepressant (Tadic et al., 2008). The reason for this is not obvious; one may speculate that the influence of IL1B on brain development is leading to different effects of various antidepressant treatments. Also, another possible mechanism may be that the shown anti-inflammatory effects of SSRI and tricyclic antidepressants (Czech and Di Benedetto, 2013) are giving rise to different immunomodulatory effects on IL-1beta; however, it is not known if the polymorphism is affecting central levels of IL-1beta.

Several genetic studies have reported associations between hippocampal grey matter volume and polymorphisms in other pro-inflammatory cytokines such as IL-6 (Baune et al., 2012a) and TNF (Baune et al., 2012b) in healthy individuals. Furthermore, grey matter volume in the hippocampus and the caudate nucleus has been reported to be negatively correlated with expression levels of immune-related genes in patients with mood disorders (Savitz et al., 2013). Moreover, plasma levels of several pro-inflammatory proteins, including IL-1beta, have been negatively associated with whole brain grey matter volume (Tsai et al., 2019). Our findings that the T allele at rs16944 and the C allele at rs1143627 were associated with increased volume in the putamen of the left hemisphere seem to be in contradiction with the notion that increased inflammation leads to a reduction in brain volume, as a haplotypic combination of these alleles has been associated with increased binding of transcription factors to the IL1B promoter in vitro (Chen et al., 2006). Further, another in vitro study found the C allele at rs1143627 to inhibit protein complex formation at this site, indicating that some transcription factors may be unable to interact with the C allele to form the transcription initiation complex (El-Omar et al., 2000).

However, the latter study found no differences in binding activity for the T allele at rs16944. Considering reports of other groups concerning this allele, such as the abovementioned lower depression severity and increased treatment response (Tadic et al., 2008; Yu et al., 2003), as well as later age of onset of depression (Hwang et al., 2009), these data together with our findings lead us to speculate whether this allele may exert a neuroprotective function. A meta-analysis also found a protective effect of the rs16944 T allele for schizophrenia (Xu and He, 2010), and this allele has been associated with higher activation of the frontal cortex in schizophrenic patients but not in controls (Patjó-Vilas et al., 2012).

The findings of this study should be interpreted in light of several limitations. First, owing to the large variety of drugs prescribed to patients in the present study, influence of medication on brain volume cannot be ruled out. For ethical reasons the subjects continued to be on treatment, and e.g. lithium has been suggested to have neuroprotective properties, significantly increasing grey matter volume (Sun et al., 2018). Also, shape alterations of the striatum have been reported in drug-naive but not drug-treated bipolar patients (Hwang et al., 2006). One can therefore not rule out medication as a confounding factor. Second, psychiatric comorbidities may affect brain volume. Third, this study did not take into account the number of years since onset of the disorder, since this was determined retrospectively and is mainly based on the patients’ self-reports. Fourth, also the number of affective episodes is determined primarily based on the patients’ self-reports and are subject to recall bias, and was therefore not corrected for. Fifth, we showed associations between genetic variations in IL1B and the volumes of various brain regions, but significant results after correction for multiple testing were obtained only for putamen in the left hemisphere. The reason for this is not obvious, and a number of studies have reported differences in volumes of various brain regions between the left and the right hemisphere (Kang et al., 2015; Wyciszewicz and Pawlak, 2014). Further studies are warranted before any conclusions might be drawn regarding possible associations between the studied gene and lateral asymmetry of the brain. And last, the strong linkage between rs16944 and rs1143627 incitates that possibly only one of these SNPs might be associated with putamen volume.

In conclusion, our findings indicate that IL1B genetic variants may be associated with the volume of the putamen, further strengthening a role of this immune system mediator on brain structure. In addition, central inflammation may influence brain plasticity since IL1-beta has been suggested to modulate synaptic transmission and long term potentiation in animal studies (Di Filippo et al., 2013). Although our results do not support the hypothesis that any of the studied polymorphisms in the genetic region coding for the pro-inflammatory cytokine IL1-beta is associated directly with bipolar disorder, we cannot rule out that different genotypes in its gene and promoter region may affect disease vulnerability in combination with other contributing factors considering the proposed involvement of this cytokine in the pathophysiology of mood disorders.

CRediT authorship contribution statement

Nina Strenn: Formal analysis, Writing - original draft. Erik Pålsson: Investigation, Data curation. Benny Liberg: Investigation, Software, Data curation. Mikael Landén: Resources, Supervision, Writing - review & editing. Agneta Ekman: Conceptualization, Supervision, Writing - review & editing.
Declarations of Competing Interest
ML declares that he has received lecture honoraria from Lundbeck pharmaceutical. Declarations of interest for all remaining authors: none.

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