Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Association between altered brain morphology and elevated peripheral endothelial markers — Implications for psychotic disorders

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ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form 2 July 2014
Accepted 10 November 2014
Available online xxxx

Keywords:
Inflammation
Endothelial markers
Basal ganglia
Brain morphology

ABSTRACT

Background: Increased inflammation, endothelial dysfunction, and structural brain abnormalities have been reported in both schizophrenia and bipolar disorder, but the relationships between these factors are unknown. We aimed to identify associations between markers of inflammatory and endothelial activation and structural brain variation in psychotic disorders.

Methods: We measured von Willebrand factor (vWf) as a marker of endothelial cell activation and six inflammatory markers (tumor necrosis factor-receptor 1, osteoprotegerin, interleukin-1-receptor antagonist, interleukin-6, C-reactive protein, CD40 ligand) in plasma and 16 brain structures obtained from MRI scans of 356 individuals (schizophrenia spectrum; n = 121, affective spectrum; n = 95, healthy control subjects; n = 140). The relationship between the inflammatory and endothelial markers and brain measurements were investigated across groups.

Results: There was a positive association ($p = 2.5 \times 10^{-4}$) between plasma levels of vWf and total volume of the basal ganglia which remained significant after correction for multiple testing. Treatment with first generation antipsychotics was associated with basal ganglia volume only ($p = 0.009$). After adjusting for diagnosis and antipsychotic medication, vWf remained significantly associated with increased basal ganglia volume ($p = 0.008$), in particular the right globus pallidus ($p = 3.7 \times 10^{-4}$). The relationship between vWf and basal ganglia volume was linear in all groups, but the intercept was significantly higher in the schizophrenia group ($df = 2$, $F = 8.2$, $p = 3.4 \times 10^{-4}$).

Conclusion: Our results show a strong positive correlation between vWf levels and basal ganglia volume, in particular globus pallidus, independent of diagnosis. vWf levels were significantly higher in schizophrenia, which could indicate a link between endothelial cell activation and basal ganglia morphology in schizophrenia patients.

1. Introduction

A growing number of magnetic resonance imaging (MRI) studies have demonstrated structural brain abnormalities in schizophrenia and bipolar disorder, particularly reduced cortical volumes and thickness, enlarged ventricles and basal ganglia, and smaller hippocampal volumes (Arnone et al., 2009; Shepherd et al., 2012; Rimol et al., 2012; Rimol et al., 2010; Ellison-Wright and Bullmore, 2010; Ellison-Wright et al., 2008). However, the underlying biological mechanisms of the structural brain changes in patients with schizophrenia or bipolar disorder remain largely unknown.

A dysfunctional cross-talk between the immune system and the central nervous system (CNS) has long been proposed as a possible mechanism for schizophrenia and bipolar disorder (Potvin et al., 2008; Goldstein et al., 2009). Several lines of evidence have implicated tissue inflammation to be involved in the pathophysiology of both disorders (Dalman et al., 2008; Leonard, 2005; Brown and Derkits, 2010; Potvin et al., 2008; Goldstein et al., 2009; Berk et al., 2011), including elevated levels of C-reactive protein (CRP), interleukin (IL)-6 and sIL-2R, as a

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http://dx.doi.org/10.1016/j.schres.2014.11.006
0920-9964/

marker of T cell activation, and soluble tumor necrosis factor receptor type 1 (sTNF-R1), von Willebrand factor (vWf) as a marker of endothelial related inflammation and osteoprotegerin (OPG) as markers of inflammation (Potvin et al., 2008; Goldstein et al., 2009; Hope et al., 2010; Hope et al., 2009). In addition, Genome-wide association studies (GWAS) have identified genes involved in immune related activity as schizophrenia risk genes (Stefansson et al., 2009; Ripke et al., 2011), further supporting immune related disease mechanisms.

An important aspect of immune related mechanisms is related to endothelial cell activation. We have previously demonstrated increased plasma levels of vWf, as a marker of endothelial cell activation, to be associated with schizophrenia and bipolar disorder (Hope et al., 2009). Furthermore, we recently reported increased blood *NOTCH4* expression in bipolar disorder indicating involvement of endothelial related inflammation in the pathophysiology (Dieset et al., 2012a). As the brain is protected by the vascular endothelium at the blood brain barrier (BBB) (Wraith and Nicholson, 2012), studies investigating peripheral biological mechanisms in schizophrenia and bipolar disorders may not necessarily provide plausible explanations for the brain alterations. Lately, however, studies have indicated that the CNS is not as immune privileged as previously thought (Wraith and Nicholson, 2012), and circulating cytokines probably penetrate the BBB to some extent (Banks et al., 1995). Quite interestingly inflammatory activity might in fact be directly involved in BBB disruption (Capuron and Miller, 2011). In accordance with this, we reported a relationship between immune abnormalities and brain morphological alterations indicating a schizophrenia specific association between certain risk variants within the MHC complex and abnormalities of the ventricular system (Agartz et al., 2011). This is in line with a recent microarray study which reported increased inflammatory mRNA expression in schizophrenia brains (Fillman et al., 2013). It remains to be seen if inflammatory markers are related to brain morphology variation in psychotic disorders. Antipsychotic medication may also affect brain morphology (Chakos et al., 1998; Ho et al., 2011) and possibly mediate inflammatory activity (Dieset et al., 2012b), which makes it a potential important confounder.

The purpose of the present study was to explore a putative relationship between plasma levels of inflammatory and endothelial cell activation markers and brain structure measures obtained with MRI in a sample of schizophrenia and bipolar spectrum patients. The rationale for selection of the inflammatory markers was to represent distinct inflammatory pathways and endothelial activation. We hypothesized that a state of low-grade inflammation and endothelial activation would be associated with brain morphological abnormalities. As there are few previous studies in this research area, we explored any association between six inflammatory and one endothelial plasma marker and 16 a priori chosen brain regions of interest including distinct measures of cortical area and thickness, as well as subcortical volumes. We then performed followup analysis of all significant associations in order to explore potential diagnostic differences and confounding factors, with a specific focus on antipsychotic medication.

2. Methods

2.1. Study design and ethics

The study was conducted as part of the Thematically Organized Psychosis (TOP) Study at Oslo University Hospital and the University of Oslo, Norway. The present sample consisted of patients and controls, all included within a particular time period (August 2003–December 2008). The TOP Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and the biobank was approved by the Norwegian Directorate of Health.

The main criteria of inclusion in the TOP Study sample are SCID-I verified DSM-IV diagnoses of psychosis within schizophrenia spectrum or affective spectrum disorders. All subjects were between 18 and 65 years and had the ability to give written informed consent and to fully comprehend the presented information about the study. Criteria of exclusion were head injury, neurological disorder, mental retardation, autoimmune and infectious disorders and malignancies. All patients underwent a standardized protocol, including psychiatric interviews such as the Positive and Negative Syndrome Scale (PANSS), Inventory of Depressive Symptoms (IDS) and Young Mania Rating Scale (YMRS). The type and amount of illicit substances and number of international units of alcohol consumed over the past two weeks before examination were recorded. In addition, all participants were screened for and diagnosed for illicit substances and alcohol using the E module in the SCID-1 manual. Medication was recorded and confirmed by information from patient records and serum measurements.

Cumulative defined daily dosage (DDD) of antipsychotics (FGA and SGA), antidepressants, mood stabilizers and lithium were calculated according to the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (hhttp://www.whocc.no/atcdd).

A total of 216 patients and 140 healthy control subjects with eligible plasma samples and MRI brain scans were included in the study. The patients were divided into two groups of either schizophrenia spectrum or affective spectrum disorder. In the group with schizophrenia spectrum diagnosis were patients diagnosed with schizophrenia ($n = 69$), schizophreniform ($n = 8$), schizoaffective disorder ($n = 14$) or psychosis not otherwise specified ($n = 30$). In the affective spectrum group were patients diagnosed with bipolar disorder I ($n = 43$), bipolar disorder II ($n = 32$), bipolar disorder not otherwise specified ($n = 6$) or depressive psychosis ($n = 14$). The age and gender matched healthy control subjects ($n = 140$) were randomly drawn from a population registry and contacted by letter inviting them to participate in the study.

2.2. Measurements of inflammatory and endothelial markers

We used the seven markers that we previously investigated for role of inflammation and endothelial activation in psychosis (Hope et al., 2010; Hope et al., 2009; Dieset et al., 2012b). The rationale for selection of the inflammatory markers was to represent distinct inflammatory pathways. IL-6, sTNF-R1 and IL-1Ra are more specifically markers of activity in the upstream inflammatory pathways, whereas hsCRP is a downstream marker of inflammation. vWf is a marker of endothelial activity and CD40L of platelet mediated inflammation, whereas OPG is a soluble member of the tumor necrosis family. Increased levels of IL-6, CRP, OPG, CD 40L and TNF-α are associated with cerebral atrophy (Jefferson et al., 2007) in an elderly population. Increased levels of CRP, IL-6, TNF-α and vWf are associated with reduced executive functioning (Heringa et al., 2014). Finally, elevated levels of IL-1RA (Lotrich et al., 2014) are associated with poorer cognitive function in bipolar disorder and elevated levels of CRP with poorer cognitive function in bipolar disorder (Dickerson et al., 2013) and schizophrenia subjects (Dickerson et al., 2007).

Plasma levels of sTNF-R1, OPG, IL-1 receptor antagonist (IL-1Ra) and IL-6 were measured using enzyme immunoassays (EIA) obtained from R&D systems (Minneapolis, MN). Plasma sCD40 ligand (sCD40L) was analyzed using EIA obtained from Bender Medsystem (Vienna Austria), whereas high sensitivity CRP (hsCRP) and vWf were measured with EIA using antibodies from DakoCytomation (Oslo, Norway). vWf levels are given as plasma concentration percent (%), where the standard curve is based on samples from healthy individuals and normal range is set to 70–130%. Intra-and interassay coefficients of variance were <10% for all assays.

2.3. MRI acquisition

All participants underwent MRI scanning on a 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional

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3-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = $1.33 \times 0.94 \times 1$ mm^3, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal to noise ratio. There was no scanner upgrade or change of instrument during the study period.

2.4. MRI post processing

The FreeSurfer software (version 4.5.0) (http://surfer.nmr.mgh.harvard.edu) was used to obtain subcortical volumetric measures and estimates of cortical thickness and areal expansion (surface area). In the sub-cortical segmentation, a neuroanatomical label is automatically assigned to each voxel in the MRI volume based on spatial location and image intensity (T1 properties; (Fischl et al., 2002)). Then, a 3-dimensional model of the cortical surface was created by using image intensities and continuity information from the entire MR volume to construct representations of the gray/white matter boundary and pial surface (Fischl et al., 1999; Dale et al., 1999). The surfaces were averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns. Each hemisphere surface consisted of approximately 160,000 vertices arranged in a triangular grid, and estimates of cortical area were obtained by computing the area of each triangle in a standardized, spherical atlas space surface tessellation. Vertex-wise estimates of relative areal expansion for each individual subject in atlas space were then computed by assigning 1/3 of the area of each triangle to each of its vertices. Cortical thickness was measured as the distance between the gray/white matter boundary and the pial surface at each vertex (Fischl and Dale, 2000). Then estimates of total frontal-, temporal-, occipital-, and parietal lobe cortical area and mean cortical thickness were calculated for the statistical analyses (Agartz et al., 2011).

2.5. Statistical analyses

In the initial analyses, total cortical thickness, total cortical area, intracranial and total brain volume, area and thickness of regional cortical measures in the four lobes (frontal, temporal, parietal, occipital), as well as hippocampus, ventricle, cerebellum and basal ganglia volume were analyzed (see Agartz et al., 2011 for more details). The effects of age and sex were regressed out from cortical structures, and age and intracranial volume from hippocampus and the subcortical structures (ventricle-, cerebellum- and basal ganglia volumes) and standardized residual values were used in the further analyses. In order to investigate whether any potential association between inflammatory markers and brain structures was influenced by patient-control status or treatment with first (FGA) or second generation antipsychotics (SGA) we performed interaction analyses. We created interaction variables between the inflammatory markers and the categorical variable patient-control and between the inflammatory markers and the continuous variables defined daily dosage (DDD) of FGA and SGA.

Due to the risk of false positives (Ioannidis, 2011), all p-values were corrected for multiple testing using Bonferroni correction for 112 tests (16 brain structures × 7 biological markers); i.e. leaving $p < 4.5 \times 10^{-4}$ as statistically significant. Only significant associations ($p < 4.5 \times 10^{-4}$) in the primary analyses were kept for further analyses; in this case only the relationship between vWf and substructures (bilaterally and subdivided by hemispheres) of the basal ganglia volume were explored in detail. As basal ganglia volume is known to be larger in schizophrenia, all analyses were adjusted for diagnoses. In addition, we investigated potential confounding effects of ethnicity, smoking, substance abuse (alcohol, cannabis, amphetamine and cocaine), total PANSS score for psychotic symptoms, total YMRS score for mania symptoms and total IDS score for depressive symptoms, GAF for general symptom and function assessment. As several studies have suggested treatment with antipsychotics to be associated with larger basal ganglia volume, we performed extensive analyses investigating the effect of medication. Categorical variables according to treatment with FGA and SGA or no treatment were created. In addition we entered DDD for all psychopharmacological medication (antipsychotics, lithium, antidepressants and mood stabilizers) as independent variables.

A total of n = 74 patients were currently not treated with any kind of antipsychotics (23 in the schizophrenia spectrum group and 51 in the affective spectrum group), n = 125 patients were currently treated with SGA, n = 11 patients were treated with FGA. Due to difficulties interpreting the result, the six (n = 6) patients who were treated with both FGA and SGA, all with schizophrenia spectrum diagnosis, were excluded from the final statistical analyses. We created a hierarchical regression model, where diagnosis was entered in the first block, FGA and SGA treatment were entered in the second block and vWf levels were entered in the third block.

Finally, we applied the standardized residuals (z-scores) adjusted for age and intracranial volume and explored the relationship between the basal ganglia volume and vWf across different diagnostic subgroups. GraphPad Prism version 6 for Windows (GraphPad Software, San Diego, CA, USA) was used to create graphs and compare the slopes and intercept of the regressed lines between the different diagnostic groups.

3. Results

3.1. Primary analyses

Plasma levels of vWf were elevated in the schizophrenia-spectrum group compared with affective-spectrum and healthy controls and TNF-R1 was significantly elevated in the schizophrenia-spectrum group compared to healthy controls (Table 1). There were significant differences across the three diagnostic groups for several of the brain structures (see Tables S1 and S2 for details). There were nominal associations between 10 brain structures and several of the inflammatory markers (Table 2). We found no interaction effect of patient vs. healthy control or being treated with FGA or SGA on the association between the inflammatory markers and the brain structures (data not shown).

3.2. vWf and basal ganglia substructures

The strongest relationship between the basal ganglia and vWf (n = 356, t = 3.7, $p = 2.5 \times 10^{-4}$) remained significant after Bonferroni correction. Treatment with FGA was associated with larger basal ganglia volume (p = 0.002), but not with vWf level. There was no significant effect of SGA, smoking, substance abuse, alcohol consumption, symptom load (according to PANSS, YMRS, IDS) or any other medication on total volume of the basal ganglia. A schizophrenia spectrum diagnosis was independently associated with both basal ganglia volume ($p < 0.001$) and vWf ($p < 0.001$) and was therefore adjusted for in all further analyses. After adjusting for diagnosis and FGA treatment, vWf remained significantly associated with basal ganglia volume (n = 350, t = 2.73, p = 0.007).

To further explore the relationship between vWf and basal ganglia volume, we investigated the substructures (putamen, globus pallidus, caudate) bilaterally and in each hemisphere. Sub-analyses revealed that FGA treatment was only associated with larger caudate (p = 0.005) and putamen (p = 0.02), not globus pallidus (p = 0.2).

After adjusting for diagnosis and antipsychotic treatment (Table 3), vWf levels were associated with larger right globus pallidus ($p = 3.7 \times 10^{-4}$), left globus pallidus (p = 0.03) and right putamen (p = 0.008). In contrast, the association between vWf and left putamen (p = 0.09) was below threshold level after adjustment for confounders. Treatment with FGA was significant in the caudate only. We found no effect of smoking, drug abuse, alcohol consumption, symptom load or

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Table 1
Demographic and clinical background of study sample.

Parameter	Schizophrenia Spectrum(1) (n = 121)		Affective Spectrum(2) (n = 95)		Healthy Controls(3) (n = 140)		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Post hoc
Age (years)*	31.0	8.0	34.8	11.8	37.2	10.4	2,3 > 1
Gender (male)	57.9		37.9		44.3		n.s
Alcohol (>15 IU/two weeks)	20.8		22.8		25.0		n.s
Tobacco (daily use)*	48.8		54.8		17.9		1,2 > 3
Cannabis (>10 times)	37.6		36.5		–		n.s
Cocaine (>10 times)	12.7		9.7		–		n.s
Antipsychotics DDD[2]	1.2	1.2	0.4	1.1	–		1 > 2
Lithium DDD	0.01	0.05	0.1	0.3	–		2 > 1
Antidepressants DDD	0.4	0.8	0.7	1.1	–		2 > 1
Mood Stabilizers DDD	0.1	0.3	0.2	0.4			2 > 1
PANSS total score**	59.6	15.6	47.2	11.6	–		1 > 2
YMRS total score	4.6	4.8	3.5	4.1	–		n.s
IDS total score	14.8	12.1	18.6	13.7	–		n.s
vWf**	113.7	52.1	95.6	52.5	82.7	46.6	1 > 2,3
TNF-R1*	1.1	0.3	1.0	0.3	0.9	0.2	1 > 3
OPG	2.5	1.4	2.6	1.1	2.5	1.0	n.s
IL-1Ra	0.8	1.3	0.6	0.8	0.6	0.8	n.s
IL-6	0.4	0.6	0.4	0.6	0.3	0.3	n.s
hsCRP	0.8	1.0	1.0	2.4	0.7	1.0	n.s
CD 40L	1.9	1.4	1.7	1.5	1.9	1.2	n.s

Table entries are mean (SD) or %. Abbreviations: SD = standard deviation, IU = international units, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale, IDS = Inventory of Depressive Symptoms, vWf = von Willebrand factor, sTNF-R1 = soluble tumor necrosis factor receptor 1, OPG = osteoprotegerin, IL-1Ra = interleukin 1 receptor antagonist, IL-6 = interleukin-6, hsCRP = high sensitivity C-reactive protein, sCD40L = soluble CD40 ligand.
[1]Patients in the mixed category fulfilled the SCID I-criteria for abuse of several substances.
[2]DDD is calculated in accordance with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (hhtp://www.whocc.no/atcdd).
Significant differences in demographic and clinical variables between the three groups were investigated using either analyses of variance (ANOVA), Kruskal–Wallis test or Pearson's Chi-Square test. Mann–Whitney *U*-test as post hoc analysis:
* $p \leq 0.01$.
** $p \leq 0.001$.

Table 2
Linear regression model investigating the relationship between inflammation- and endothelial markers and brain structures.

	β	S.E	t	p
Cortical thickness				
hsCRP	−0.1	0.0	−2.8	0.01
Cortical area				
IL-1Ra	0.1	1362.0	2.1	0.03
OPG	−0.1	579.0	−2.4	0.02
Frontal lobe thickness				
hsCRP	−0.1	0.1	−2.7	0.01
Temporal lobe thickness				
hsCRP	−0.1	0.1	−2.3	0.02
Temporal lobe area				
OPG	−0.2	132.8	−3.3	0.01
IL-1Ra	0.1	284.4	2.3	0.03
hsCRP	0.1	99.0	2.0	0.04
Parietal lobe thickness				
hsCRP	−0.1	0.0	−2.4	0.02
Occipital lobe area				
hsCRP	0.1	76.6	2.1	0.04
Ventricles				
CD40L	0.1	0.0	2.1	0.04
Hippocampus				
OPG	−0.1	29.0	−1.9	0.05
Basal ganglia				
TNF-R1	0.1	307.0	2.7	0.01
vWf	0.1	1.7	0.1	$\mathbf{2.5 \times 10^{-4}}$

Abbreviations: hsCRP = high sensitivity C-reactive protein, sTNF-R1 = soluble tumor necrosis factor receptor 1, vWf = von Willebrand factor, IL-Ra = interleukin 1 receptor antagonist, CD 40L = CD 40 ligand, OPG = osteoprotegerin.
Only the results that were nominally significant are shown in the table. Bold values remained significant after Bonferroni correction for 112 tests. Due to skewed data, analysis are performed and presented in log-transformed format for the ventricles. The analyses for cortical structures are adjusted for sex and age, the analyses for subcortical structures are adjusted for total intracranial volume and age.

any other medication on the relationship between levels of vWf and substructures in the basal ganglia.

3.3. vWf and basal ganglia volume across diagnostic groups

The regression lines showed that the relationship between vWf and basal ganglia volume was linear in all groups (compared slopes; df = 2, F = 0.6, p = 0.5). There was a highly significant difference in the intercept (compared intercept; df = 2, F = 8.2, $p = 3.0 \times 10^{-4}$) in the schizophrenia spectrum group compared with the affective spectrum and the healthy control group (Fig. 1), i.e. any given value of vWf was associated with larger basal ganglia volume in schizophrenia compared with healthy controls and bipolar disorder.

4. Discussion

We report a strong linear association between plasma levels of vWf and basal ganglia volume in patients with psychotic disorders and healthy controls. This association remained significant after adjusting for a range of confounders, including antipsychotic medication, substance abuse, alcohol consumption and diagnosis. Further, any given level of vWf is associated with larger basal ganglia volumes in schizophrenia. In addition, we report nominally significant associations between six other inflammatory markers and brain morphology. This is, to the best of our knowledge, the first study to show a relationship between vWf and brain structures in a large sample with psychotic disorders.

Inflammatory cytokines may play a role as neurotransmitters and there are several ways as to which they can reach the brain: they might pass through the blood brain barrier either through leaky regions, by passive transfusion or by active transport (Haroon et al., 2012). The mechanistic relationship between brain structure and plasma levels of inflammatory and endothelial markers might also be of genetic origin. Several studies have shown associations between polymorphisms in immune-related genes and structural brain alterations (McAllister, 2014; Agartz et al., 2011). One other possible explanation might thus be that some subjects have a genetic predisposition that cause brain alterations due to inflammatory processes in the CNS as well as increased inflammation in the periphery. A third possible explanation is that infections in the mother during gestational life initiate microglia activation in the fetus which in genetically vulnerable subjects. Microglia activity is later re-activated by stress or new infections and ultimately causes changes in the brain resulting in a psychotic disorder (Bergink et al., 2014).

The mechanisms underlying the association between elevated plasma levels of vWf and increased basal ganglia volume are unclear. The basal ganglia are complex subcortical structures involved in control of the motor system, executive and emotional function as well as salience, motivation and learning (Graybiel et al., 1994; Packard and Knowlton, 2002; Kapur, 2003), and contain dopaminergic, glutaminergic, histaminergic and GABAergic neurons (Brown et al., 2001; Graybiel, 2005). The basal ganglia are highly vascularized (Hegde et al., 2011) with a high density of endothelial cells, which store and synthesize vWf. Accordingly, the expression of vWf is dense in the basal ganglia, and in particular within the globus pallidus (gene expression z-scores up to 3.9 in right globus pallidus; www.brain-map.org). Interestingly we

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Table 3
Hierarchical multiple regression investigating potential predictors of substructure volumes in the basal ganglia.

	Globus pallidus (age and ICV adjusted)						Putamen (age and ICV adjusted)						Caudate (age and ICV adjusted)					
	Right			Left			Right			Left			Right			Left		
	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p	β	t	p
Schizophrenia diagnosis	0.37	2.69	**0.01**	0.42	3.01	**0.003**	0.003	3.12	**0.002**	0.46	3.34	**0.001**	0.19	1.37	0.17	0.18	1.27	0.21
FGA	0.06	0.21	0.84	0.28	0.92	0.36	0.49	1.58	0.11	0.42	1.36	0.18	0.93	3.00	**0.003**	0.67	2.14	**0.03**
SGA	−0.01	−0.10	0.92	−0.11	−0.84	0.40	−0.19	−1.38	0.17	−0.21	−1.52	0.13	0.14	1.05	0.29	0.11	0.79	0.43
von Willebrand factor	0.04	3.69	$\mathbf{3.7 \times 10^{-4}}$	0.01	2.17	**0.03**	0.003	2.65	**0.008**	0.002	1.70	0.09	0.002	1.65	0.10	0.001	1.19	0.24

Abbreviations: FGA = first generation antipsychotics, SGA = second generation antipsychotics, ICV = intracranial volume.
Hierarchical multiple regression model with age and ICV adjusted brain measures as dependent variables and forced entry of diagnosis in block one, medication in block two and von Willebrand factors levels in block three as independent variables. Significant values in bold.

found globus pallidus to be the structure most strongly associated with vWf plasma levels. We can speculate that the strong and independent association to vWf could reflect increased vascularization and edema in the basal ganglia, and possibly also involve an interaction between inflammation and endothelial cells (Paulus et al., 2011). However, this needs to be clarified in experimental studies.

We found elevated levels of vWf as well as increased basal ganglia volumes in schizophrenia patients compared to healthy controls and patients with affective spectrum disorders. There was no interaction effect between schizophrenia and vWf levels on basal ganglia volume. The regression lines were parallel across all diagnostic groups, which supports that the relationship between basal ganglia volume and vWf is biologically valid. However, the strongly significant difference in the intercept indicates that any given level of vWf is associated with larger basal ganglia volumes in schizophrenia compared with affective spectrum disorder and healthy controls. There are several potential explanations for this. Firstly, endothelial dysfunction might be one of many causes contributing to increased basal ganglia volume in schizophrenia. Secondly, there might be other factors such as drugs or other inflammatory markers that interact and enhance the effect of vWf on the basal ganglia volume specifically in schizophrenia. Finally, schizophrenia patients might have genetic dispositions which make them particularly vulnerable in terms of pathophysiological processes involving endothelial dysfunction and inflammation.

Increased volume of the basal ganglia has repeatedly been reported in MRI studies of schizophrenia (Ellison-Wright and Bullmore, 2010; Rimol et al., 2010), and dysfunctional neural circuits in the basal ganglia have been suggested to underlie subtle movement abnormalities and mild cognitive impairments of the disorder (Perez-Costas et al., 2010; Graybiel et al., 1994). Interestingly, some studies have shown a relationship between elevated plasma levels of vWf and cognitive decline (Quinn et al., 2011; Heringa et al., 2014). Positron emission tomography (PET) studies have reported increased blood flow to the basal ganglia, particularly to the globus pallidus, in schizophrenia (Early et al., 1987).

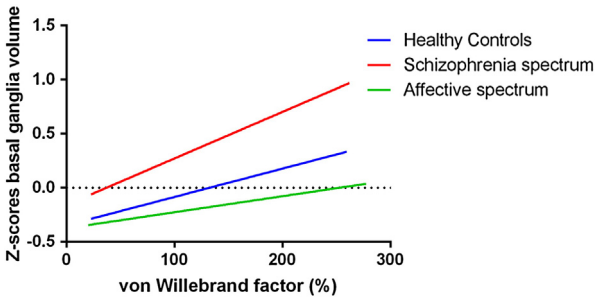

Fig. 1. Regression line graph displaying the relationship between basal ganglia volume and von Willebrand factor across diagnostic groups. Plotted along the y-axis are extracted basal ganglia volume values from FreeSurfer displayed in standardized units (z-scores) adjusted for age and intracranial volume. Plotted along the x-axis are plasma von Willebrand factor levels (%).

Moreover, the basal ganglia have a high concentration of dopamine receptors. Abnormal dopaminergic activity in the striatum has been postulated as a disease mechanism for schizophrenia ever since the effect of dopamine (D2) blockade of antipsychotics was discovered (Farde et al., 1988; Carlsson and Carlsson, 1990b; Carlsson et al., 1999; Carlsson and Carlsson, 1990a). Thus, a possible explanation for the association between vWf and basal ganglia in schizophrenia might be related to the extensive endogenous dopamine activity in the basal ganglia in schizophrenia patients (Farde et al., 1988). This is supported by animal studies showing that dopamine treatment (L-dopa) in rats induces endothelial cell proliferation creating new and immature vasculature in the basal ganglia with defective BBB ultimately resulting in leakage of e.g. albumin into the brain (Westin et al., 2006). The present findings of a strong relationship between elevated vWf levels and increased basal ganglia volume could thus be a secondary effect of a dopamine-induced endothelial cell action with a dysfunctional endothelium of the basal ganglia as a consequence.

Quite recently, a review of all available longitudinal MRI studies (n = 13) investigating the effect of antipsychotic monotherapy on basal ganglia volume concluded that antipsychotic treatment (FGA and SGA) is not associated with an increase in basal ganglia volume (Ebdrup et al., 2013). Nevertheless, as antipsychotic medication (FGA in particular) has been linked to larger basal ganglia volume in case control studies (Navari and Dazzan, 2009; Ho et al., 2011), the potential impact of medication must be taken into account. In line with some other studies (Corson et al., 1999; Lieberman et al., 2005), we found that treatment with FGA was associated with larger caudate volume in our sample. Interestingly, our analyses revealed that vWf was a stronger predictor of globus pallidus and putamen volume than antipsychotic treatment, both FGA and SGA. Several studies on other groups of patients and healthy controls have reported that peripheral inflammation is associated with increased metabolism in the basal ganglia causing symptoms often seen in schizophrenia, such as fatigue, anhedonia, loss of concentration and reduced energy (Capuron and Miller, 2011; Banks et al., 2002; Brydon et al., 2008; Eisenberger et al., 2010). Note, however, that our data do not exclude an effect of antipsychotic treatment on basal ganglia volume. Our results rather suggest that there might be several mechanisms playing different roles in the basal ganglia substructures and that inflammatory mechanisms might be involved in basal ganglia morphology.

There are some limitations to the present study. Firstly, as our study has a case control design, the results do not reveal the causal direction of the effect and these findings need to be replicated in larger independent samples. Furthermore, we do not know if these markers are static or changing during the course of the illness which is an important question that calls for longitudinal studies. Secondly, as our approach was exploratory we chose a conservative Bonferroni procedure for correction for multiple testing, which might have generated type-II errors. Thus, there might be interesting relationships between some of the other six inflammatory markers and brain morphology that deserve further attention. Thirdly, although we adjusted the analyses for a range of

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potential confounders, there still might be other factors (e.g. genetic, toxins) not taken into account. Although we did control for medication, we cannot rule out any medication effect. Fourth, we acknowledge that plasma biomarkers are not directly reflecting CNS activity, but could also be affected by other tissues. Thus, it is difficult to draw firm conclusions about brain function from measurements of peripheral markers in schizophrenia. On the other hand, a recent study has shown a strong correlation between peripheral markers and markers measured in post-mortem schizophrenia brains (Harris et al., 2012). Furthermore, psychotic disorders are increasingly recognized as systemic diseases (Kirkpatrick, 2009) and assuming that inflammatory cytokines to some extent pass the blood brain barrier, investigating peripheral activity might provide useful information regarding disease mechanisms in psychotic disorders. Finally, we recognize that investigating a more homogenous group might have strengthened our results.

In summary, our results indicate a strong association between elevated vWf levels and increased volumes of the basal ganglia, in particular the globus pallidus in patients with psychotic disorders and healthy controls. Elevated vWf levels explained more of the variance in the globus pallidus and putamen volume than antipsychotic treatment. As schizophrenia patients demonstrated significantly elevated levels of vWf, our findings suggest that endothelial related inflammation may contribute to the increased globus pallidus volume and putamen volume observed in this group of patients.

Financial disclosures

Anders M. Dale is a founder and holds equity in CorTechs Labs, and also serves on the Scientific Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. Ole A. Andreassen has received speaker honorarium from Lilly, Lundbeck, GSK in the last two years. ID, UKH, IM, JIR, TU, SH, SD, PA, IA and ID report no conflict of interest.

Contributors

Ingrid Dieset conceived the study, acquired and analyzed the data and drafted the manuscript. Unn Haukvik contributed with the study design, data acquisition, quality control and analyses of MRI data, she also contributed in the drafting process of the manuscript. Ingrid Melle, Jan Ivar Røssberg, Sigrun Hope and Ingrid Agartz and contributed with study design, data acquisition, analyses of data and drafting of the manuscript. Pål Aukrust and Thor Ueland contributed to the study conception, inflammation marker analyses, interpretation of data, as well as drafting the manuscript. Srdjan Djurovic contributed to immune data acquisition, as well as performing extensive quality control and giving advice during the drafting process of the manuscript. Anders Dale has developed the software (Freesurfer) used for analyses of the imaging data, in addition he contributed to the quality control of the MRI data. Ole A. Andreassen participated in conceiving the study, he acquired and supervised the data analyses. As senior author, he was also extensively involved in the drafting process of the manuscript.

Funding source

The study was supported by grants from: the Research Council of Norway (167153/V50, 163070/V50), South-Eastern and Western Norway Health Authority, Oslo University Hospital (2004123, 2007050) and the University of Oslo and KG Jebsen Foundation. The funding sources had no further role in study design, in the collection, analysis and interpretation of data, or in the writing of the report and in the decision to submit the paper for publication.

Acknowledgements

We thank patients and controls for their participation in the study, and the health professionals who facilitated our work. We also wish to thank Thomas H. Bjella and Eivind Bakken for the skilful technical assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.11.006.

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