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Research Paper

The impact of schizophrenia and intelligence on the relationship between age and brain volume

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ABSTRACT

Age has been shown to have an impact on both grey (GM) and white matter (WM) volume, with a steeper slope of age-related decline in schizophrenia compared to healthy controls. In schizophrenia, the relation between age and brain volume is further complicated by factors such as lower intelligence, antipsychotic medication, and cannabis use, all of which have been shown to have independent effects on brain volume.

In a study of first-episode, antipsychotic-naïve schizophrenia patients (N = 54) and healthy controls (N = 56), we examined the effects of age on whole brain measures of GM and WM volume, and whether these relationships were moderated by schizophrenia and intelligence (IQ). Secondarily, we examined lifetime cannabis use as a moderator of the relationship between age and brain volume.

Schizophrenia patients had lower GM volumes than healthy controls but did not differ on WM volume. We found an age effect on GM indicating that increasing age was associated with lower GM volumes, which did not differ between groups. IQ did not have a direct effect on GM, but showed a trend-level interaction with age, suggesting a greater impact of age with lower IQ. There were no age effects on WM volume, but a direct effect of IQ, with higher IQ showing an association with larger WM volume. Lifetime cannabis use did not alter these findings significantly.

This study points to effects of schizophrenia on GM early in the illness, before antipsychotic treatment is initiated, suggesting that WM changes may occur later in the disease process.

1. Introduction

Patients with schizophrenia have been found to have a steeper regression slope of age-related changes in brain volume compared to healthy people (Hulshoff Pol et al., 2002). A meta-analysis of longitudinal studies in schizophrenia reported progressive changes in both grey (GM) and white matter (WM) volume over time (Olabi et al., 2011). This progressive loss of brain volume was found to be particularly steep in the first years after illness onset, suggesting that the underlying pathological and/or environmental factors may be accelerated in the early stages of the illness (Andreasen et al., 2011; Sun et al., 2009; Vita et al., 2012). The trajectory of brain volume changes with age in schizophrenia appears to be more severe than that related to normal aging before 45 years of age, after which brain volume in patients appears to decrease at a normal rate (Van Haren et al., 2008). Further, differences in trajectories of GM and WM over age suggest that reductions in WM occur later than in GM (Cropley et al., 2017).

Brain volume is affected by several genetic and environmental factors, the relative impact of which changes with age (Batouli et al., 2014). During normal brain maturation, there is an increase of total brain volume throughout childhood, with evidence of a gradual decrease after age 13, relative stability in young adulthood, and a slight decrease starting again in the mid-30s, which accelerates in late life, from around age 60 (Hedman et al., 2012). The timing of normal maturation differs between GM and WM, with a peak of GM volume in the mid-20s and of WM in the late 30s (Lebel et al., 2012). The relationship

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between age and brain volume in schizophrenia is complex, since environmental factors, including antipsychotic medication and cannabis use, also have independent effects on brain structure and function (Van Van Haren et al., 2013). Reductions in global brain volume have been found in first-episode, medication-naïve patients with schizophrenia, but to a smaller extent than in medicated patients, indicating that brain volume reductions are present at illness onset, with evidence of further progressive loss due to the effects of the illness and/or impact of treatment (Ansell et al., 2015; Haijma et al., 2013).

Another factor related to brain volume changes with age is intelligence (IQ). In healthy people a significant positive correlation between intelligence and brain volume is found (McDaniel, 2005), with the covariance ranging from small (Pietschnig et al., 2015) to substantial (Ritchie, 2015). A similar, and perhaps stronger relationship has been found in schizophrenia patients (Rais et al., 2012). Throughout normal brain development and maturation, brain volume increase with age is positively correlated with IQ (Brans et al., 2010; Shaw et al., 2006). Similarly, decrease in brain volume across adulthood is negatively related to IQ, with evidence of shared heritability of brain volume changes and IQ across the lifespan (Brans et al., 2010; Brouwer et al., 2014). In schizophrenia, age-related decrease in brain volume has been found to be related to relative progression of IQ deficits (Kubota et al., 2015), but it is difficult to disentangle this relationship from medication effects.

In the present study, we examined antipsychotic-naïve first-episode schizophrenia patients at first presentation, thus avoiding the confounding effects of medication and chronicity. The primary aim was to examine if the effect of age on total GM and WM volumes is moderated by schizophrenia and intelligence, or their interaction at this early stage of the illness. A secondary aim was to examine the contribution of lifetime cannabis use on any age-related effects of first-episode schizophrenia and intelligence on brain volume. These aims were examined in a cross-sectional study of antipsychotic-naïve first-episode schizophrenia patients and healthy controls. Based on previous findings we hypothesized a more pronounced effect of age on GM than WM volume in first episode schizophrenia patients compared to healthy controls, and expected an interaction between the effects of schizophrenia and lower intelligence on GM volume.

2. Materials and methods

The study was approved by the Danish National Committee on Biomedical Research Ethics (H-D-2008-088) and the Danish Data Protection Agency (2008-41-2701) and conducted in accordance with the Declaration of Helsinki II. All participants provided written informed consent before inclusion.

As part of a multimodal cohort study, both in- and out-patients aged 18 to 45 years presenting with a first-episode of schizophrenia were referred from Mental Health Services in the Capital Region of Denmark from December 2008 to April 2014. The cohort was initially presented in Nielsen et al. (2012), and there is partial overlap with aspects of data presented on cortical thickness, WM and psychotic symptoms, and machine learning (Bak et al., 2017; Ebdrup et al., 2016; Jessen et al., 2018), see also www.cinsr.dk for other publications from this cohort. Patients fulfilling criteria of an ICD-10 diagnosis of schizophrenia were included. Healthy controls were recruited from the community through a webpage (www.forsoegsperson.dk). Exclusion criteria for all participants were: Any current or previous treatment with antipsychotic medication; treatment with antidepressants within the past month; serious somatic or neurological illness; a history of head injury with loss of consciousness > 5 min; and a current ICD-10 diagnosis of drug dependence. Current occasional drug use was accepted (assessed by interview and urine screening). Additional exclusion criteria specific to healthy controls were: Previous or current psychiatric illness, or psychiatric illness in first-degree relatives. Benzodiazepines were not allowed on days of examinations.

Table 1
Demographic and clinical data for antipsychotic-naive schizophrenia patients and healthy controls. Results from analyses of group differences.

	Antipsychotic-naïve schizophrenia patients	Healthy controls
Demographic data		
Mean age in years; mean (SD)	24.69 (5.93)	24.91 (5.61)
Male gender; N (%)	31 (57)	33 (59)
Years of education; mean (SD)**	12.23 (2.49)	14.64 (2.57)
Parental SES (A/B/C)[a]	11/30/10	17/28/10
Cannabis (0/1/2/3)[a,**]	11/28/11/4	28/21/5/0
IQ; mean z-score (SD)**	−1.04 (1.63)	0.00 (1.00)
Clinical data		
PANSS positive; mean (SD)	20.35 (4.1)	
PANSS negative; mean (SD)	20.96 (7.55)	
PANSS general, mean (SD)	42.02 (8.90)	
PANSS total; mean (SD)	83.33 (16.88)	

No significant group differences: Gender ($\chi^2 = 0.026$, df = 1, $p = 0.872$); Parental SES ($\chi^2 = 1.205$, df = 2, $p = 0.547$).

[a] N varies due to missing data: Parental SES (patient N = 51/control N = 55); Cannabis use (patient N = 54/control N = 54).

** Group differences $p \leq 0.001$: Years of education ($F(108) = 0.513$, $p < 0.00001$); IQ ($F(86.691) = 10.189$, $p < 0.001$); Cannabis use (Fisher's exact test = 14.359, $p = 0.001$).

Diagnosis at inclusion was based on the diagnostic interview Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) (SCAN), version 2.1. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Lifetime cannabis use was rated on a 5-point ordinal scale (0 = Never tried, 1 = Tried a few times, 2 = Use regularly, 3 = Abuse, 4 = Dependency).

A total of 69 patients and 67 healthy controls were recruited. Fifty-four patients and 56 healthy controls had full magnetic resonance imaging (MR) and Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) datasets and were included in the present analyses. The healthy controls were matched to patients on gender, age and parental socioeconomic status, thus there were no significant group differences on these measures (see Table 1).

Four subtests from the Danish version of the WAIS-III (Wechsler, 1997); Vocabulary, Similarities, Block Design and Matrix Reasoning were combined to provide a measure of intelligence quotient (IQ). These 4 subtests have been shown to correlate strongly with Full Scale IQ (Axelrod, 2002). Raw scores were normalized to z-scores using the healthy control group as reference (Table 1).

Structural MR was performed using a Phillips Achieva 3.0 whole body MRI scanner (Phillips Healthcare) with an 8-channel SENSE head coil (Invivo). Three-dimensional high-resolution T1 weighted images were acquired with repetition time 10 msec, echo time 4.6 ms, flip angle 8°, and voxel size 0.79 × 0.79 × 0.80 mm^3. Total GM and WM volumes were estimated using SIENAX, part of the FSL software (Table 2). This procedure estimates raw brain volumes as well as brain volumes after spatially normalizing the intracranial volume (ICV) to

Table 2
Grey and white matter volume in antipsychotic-naive schizophrenia patients and healthy controls.

Volume in mm^3	Antipsychotic-naïve schizophrenia patients N = 54	Healthy controls N = 56
Grey matter volume; mean (SD)	862.91 (49.79)	882.10 (52.59)
White matter volume; mean (SD)	755.67 (39.47)	763.02 (47.72)

that of a reference space. In the present work we primarily used the normalized brain volumes in order to minimize the effects of gender related to body-size. Gender was found to have no significant effect on normalized brain volumes and was not entered into the analyses. PANSS symptom scores and duration of untreated illness did not correlate with GM or WM volumes in the patient group and were not included in analyses. Assessments (e.g. inclusion interviews, psychopathology ratings, MR scans and cognitive tests) were carried out within a 2-week period before treatment initiation.

All statistical analyses were carried out using SPSS 24.0. All analyses used two-tailed levels of significance set at $p < 0.05$. Normality was examined using the Shapiro-Wilk test of normality. Differences in characteristics between groups were tested with *t*-tests for continuous data and Pearson's χ^2 for nominal data. To examine whether group (schizophrenia vs healthy controls) and intelligence moderated the effect of age on brain volume we applied a multiple regression model. The main effects of age, IQ and group were estimated along with the moderating 2-way interactions (age * IQ, and age * group) and 3-way interactions (age * IQ * group). The analyses were performed twice, using total GM or total WM. Parameter values were estimated with bootstrap sampling (10,000 samples) on centered variables. In secondary analyses we examined the effect of including cannabis use in the model (adding main effect of cannabis use, age * cannabis use, and age * cannabis use * group interactions).

3. Results

The patient sample was 57% male, mean age 24.7 ± 5.9 years; the matched healthy control sample was 59% male, mean age 24.9 ± 5.6 years. As expected, healthy controls had significantly more years of education compared to patients ($F(108) = 0.513$, $p < 0.001$). With a mean total PANSS score of 83.3 ± 16.9, the patients were 'markedly ill' (Leucht et al., 2005). IQ was significantly lower in patients compared to controls with an average z-score of −1.04 SD ($F(86.691) = 10.189$, $p < 0.001$), which is similar to previous first-episode studies (Mesholam-Gately et al., 2009). Lifetime cannabis use was significantly more prevalent in the patient group than in the healthy controls (Fisher's exact test = 14.359, $p = 0.001$).

There was a significant effect of age ($p < 0.001$) and group ($p = 0.04$) on GM volume (Fig. 1). While IQ did not have an independent effect on grey matter, there was a trend level age*IQ interaction ($p = 0.07$). The interaction suggested a steeper negative slope between GM and age with lower IQ scores. There was no group*age interaction (Table 3). There was no direct effect of cannabis use on GM volume and no significant interaction by group.

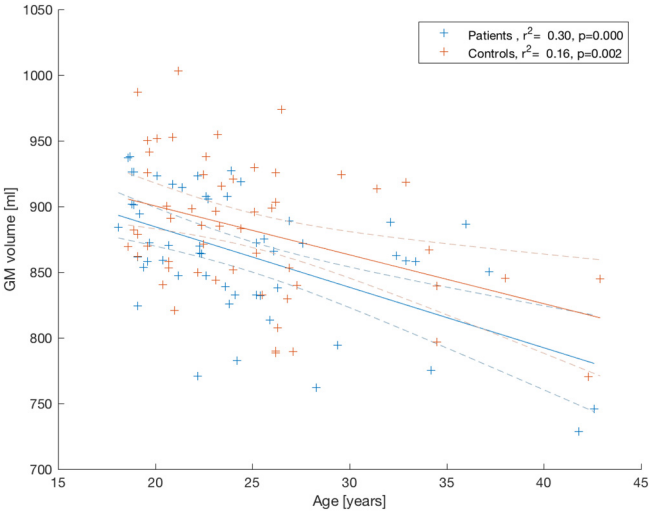


Fig. 1. Effect of age on grey matter volume in schizophrenia patients and healthy controls.

There was no direct effect of age or group on WM, but a significant effect of IQ ($p = 0.04$) (Figs. 2 and 3). There were no significant interactions (Table 3). Cannabis did not contribute to the model and there were no direct or interaction effects of cannabis on WM.

4. Discussion

In this study of antipsychotic-naïve first-episode patients with schizophrenia, we examined the effect of age at first presentation on global measures of GM and WM and examined whether this effect was moderated by IQ. Patients had lower GM volumes compared with healthy controls. Increasing age was associated with a significantly lower GM volume in both patients and controls, with no significant difference between groups in this relationship. While IQ had no significant effect on GM, there was a trend-level IQ by age effect on GM, suggesting that increasing age had a greater impact on GM volume in those with lower IQ. There were no differences between patients and controls for WM volume and there were no significant effects by age. There was, however, an effect of IQ on WM, which did not differ between groups, with higher IQ showing an association with greater WM volume. No relationships were observed for cannabis with either GM or WM volumes in patients or controls.

Our findings showing a different pattern for GM and WM by age at illness onset are consistent with the findings of Cropley et al., in which GM loss in schizophrenia was greatest in early adulthood (mid-20s onward), while WM loss was most severe at older ages (30s onward) (Cropley et al., 2017). Nevertheless, we would need a larger sample of patients with an onset of illness after their mid-30s to be able to conclude if WM loss is present in antipsychotic-naïve patients at later ages of onset. This also accords with differences in timing of maturational changes of GM that extend into the mid-20s compared to white matter where changes continue into the 4th decade (Lebel et al., 2012). The effect of age and group, and trend-level interaction effect of age and IQ on GM may also support Kubota et al., who found longitudinal, relative improvement in IQ to be positively associated with brain volume in schizophrenia (Kubota et al., 2015).

Only IQ had a direct effect on WM, which was consistent regardless of cannabis use. Another study of antipsychotic-naïve patients with schizophrenia found similar results, with a positive association between IQ and WM and total brain volume, but not GM (Rais et al., 2012). Because of the difference in IQ between the groups, where no healthy controls scored in the very low range, part of the interaction between IQ and WM may be primarily related to schizophrenia. However, we did not find any group interactions on the relation between IQ and WM, suggesting that this relationship was not only driven by the patients. Further, in a study examining GM to WM ratio by age, Bartzokis et al. (Bartzokis et al., 2003) found group differences in the GM to WM ratio that increased with age and suggested this was due to insufficient white matter growth in schizophrenia patients compared to healthy controls. Differences in the trajectories between GM and WM are observed in key regions implicated in schizophrenia, especially involving association cortices that mature in adolescence and early adulthood, involving temporal and frontal regions. Importantly, while GM changes occur into early adulthood (Gogtay et al., 2004), WM myelination in these regions continues into mid-adulthood (Benes et al., 1994). This indicates that assessing structural changes at illness onset should be considered in the context of the timing of normal brain maturational changes in GM and WM in different regions of the brain (Gogtay et al., 2011).

A major strength of the study is the inclusion of only antipsychotic-naïve patients with first-episode schizophrenia. The antipsychotic-naïve definition was strict, not allowing for a single dose of antipsychotic medication, thus avoiding the confounding effects of antipsychotic medication on brain structure. Another strength is the wider age range for inclusion (18–45 years) than most other first-episode adult samples, allowing a more comprehensive examination across age of illness onset.

Table 3
Bootstrap parameter estimates.

Age, group and IQ effects on GM and WM volume				
Dependent variables		B (SD)	*p*-Value	BCa[d] 95% confidence interval
Grey matter	Intercept[a]	862.25 (5.84)	< 0.001	(851.22, 871.59)
	Group[b]	18.72 (9.11)	0.04	(−0.96, 42.35)
	Age[c]	−4.09 (1.12)	< 0.001	(−6.28, −2.28)
	IQ[c]	2.57 (3.57)	0.46	(−4.16, 8.98)
	Age ∗ group	0.30 (1.76)	0.85	(−3.45, 5.63)
	Age ∗ IQ	1.03 (0.68)	0.07	(−0.59, 2.24)
	Age ∗ group ∗ IQ	−0.60 (1.80)	0.57	(−4.27, 0.73)
White matter	Intercept	757.89 (5.51)	< 0.001	(747.17, 770.51)
	Group[b]	1.56 (9.01)	0.90	(−14.16, 13.16)
	Age[c]	−0.43 (1.50)	0.77	(−2.80, 3.38)
	IQ[c]	6.47 (3.10)	0.04	(−0.67, 13.50)
	Age ∗ group	2.87 (2.20)	0.15	(−0.97, 4.84)
	Age ∗ IQ	0.73 (0.71)	0.18	(−0.53, 2.53)
	Age ∗ group ∗ IQ	−0.59 (2.08)	0.66	(−4.13, 6.25)

[a] GM and WM volumes were spatially normalized, corrected for ICV and are reported in mm^3.
[b] Group (0 = healthy controls; 1 = schizophrenia patients), i.e. positive effects of group indicate larger volumes in controls compared to patients.
[c] Age and IQ were centered in analyses.
[d] BCa = Bias-corrected and accelerated bootstrap interval.

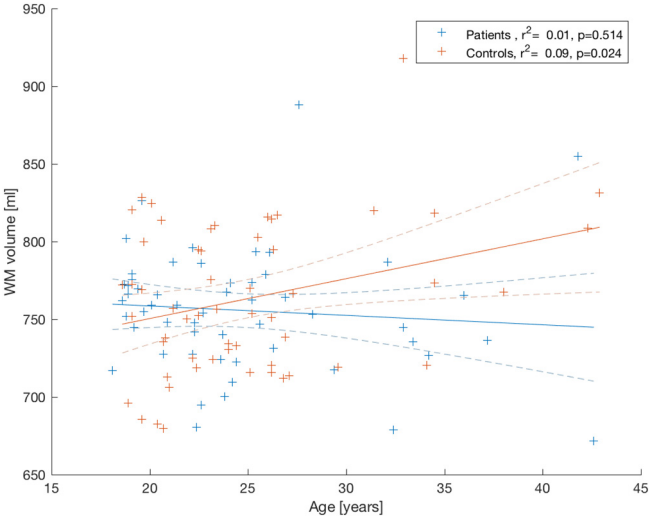


Fig. 2. Effect of age on white matter volume in schizophrenia patients and healthy controls.

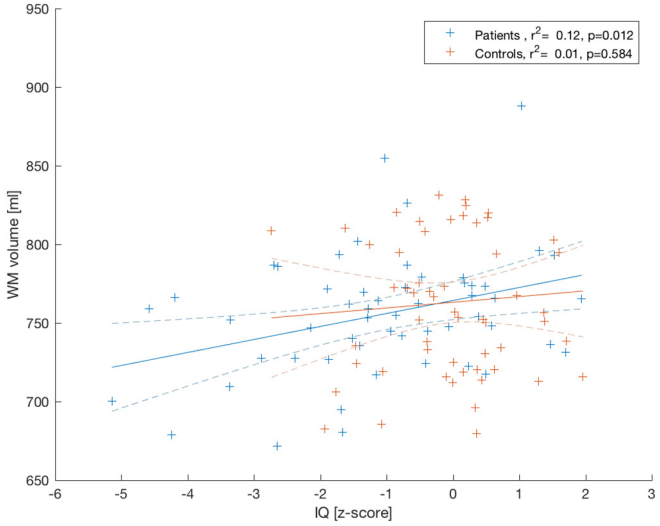


Fig. 3. Effect of IQ on white matter volume in schizophrenia patients and healthy controls.

It should be noted that this first-episode study was skewed towards the younger ages of onset, reflecting the peak age of illness onset in the early 20s. We did not have many first episode cases after age 40 years, thus the linear statistical model applied may not have been able to sufficiently address the resulting uneven variance across the age distribution. While the results reflect effects of age of onset within an age range that captures most of the incident cases, future studies should include both younger illness onset in adolescence (< 18 years) and older ages of illness onset (> 45 years), which would also enable examination of the impact of age of onset and interactions with illness and IQ on the developing and aging brain, respectively. Also, following these patients and controls longitudinally will allow examination of trajectories and the dynamic relationships between age, illness, IQ and brain structure from the antipsychotic-naïve state across the course of illness.

A limitation to the study was the relatively small sample size, which is explained by the fact that antipsychotic-naïve first-episode schizophrenia patients are challenging to recruit. We therefore cannot exclude the possibility that some of the negative findings may be due to a type 2 error. The whole brain GM and WM volume outcome measures used in this study allowed for an examination of the global effects of age of onset and interactions with illness, IQ, and cannabis. In order to investigate the global vs regional nature of these effects and interactions, a more detailed, e.g. a region of interest (ROI) approach would be required. However, ROI analyses would require a larger sample size.

Cannabis use did not have an independent effect on the whole brain GM or WM measures examined in this study, which may in part be due to our exclusion of patients with diagnosed drug dependency and the measure of lifetime use applied in this study. The cumulative dose of cannabis use has been found to have an impact on GM in non-psychotic heavy users (Yücel et al., 2008), while the age of onset of cannabis use may be more relevant for effects on WM (Zalesky et al., 2012). It is also possible that a more specific ROI approach to GM and WM may have yielded different results, in terms of effects of cannabis, age, and IQ. Future studies should also examine subcortical regions, especially the hippocampal formation, as these regions appear to be specifically affected by cannabis (Ebdrup et al., 2010; Solowij et al., 2013; Yücel et al., 2008; Zalesky et al., 2012).

In conclusion, this study found differences between first-episode, antipsychotic-naïve schizophrenia patients and healthy controls on GM, a general impact of age on GM, and that intelligence has an impact on

WM in both patients and healthy controls.

Contributors

BG and BF designed the study. MHJ, NB, CP, and BF conducted the literature review. MHJ, MØN, ER, BG, BE and BF were involved in the data collection. MHJ wrote the first draft of the paper. NB and BF analyzed the data. MHJ, NB, BF and CP revised and edited subsequent drafts after co-author comments. All authors commented on drafts of the paper, contributed to and have approved the final version of the manuscript.

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