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INFLUENCE OF PSYCHOTIC EPISODES ON GREY MATTER VOLUME CHANGES IN PATIENTS WITH SCHIZOPHRENIA

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SUMMARY

Background: *Schizophrenia is a severe illness whose clinical course is characterized by various numbers of psychotic episodes (PE). The neurotoxic hypothesis (NH) of schizophrenia assumes that psychosis is biologically toxic. The aim of the study was to investigate whether schizophrenia patients (SP) with multiple PE have greater grey matter volume (GMV) reduction compared to SP with fewer PE.*

Subjects and methods: *We enrolled 106 adult SP and 63 healthy controls. Demographic and clinical data were collected and statistically analysed for all included subjects. Magnetic resonance imaging (MRI) of the brain was acquired on a 1.5 T scanner. SP were grouped according to the number of PE into a group with up to 3 PE (SCHG-1) and with 4 or more PE (SCHG-2). SCHG-1 was further subdivided into two groups regarding to disease duration (DD). Voxel-based morphometry (VBM) analyses were performed between SP groups as well as between SP groups and the healthy controls group (HCG).*

Results: *No relevant GMV differences were detected between SP groups. Comparison between HCG and SCHG-1 showed only 3 regions with reduced GMV, while multiple regions with reduced GMV were detected when comparing HCG and SCHG-2.*

Conclusions*: GMV reduction in schizophrenia varies depending on the number of PE when compared to HCG, regardless of disease duration (DD), but PE is not the only contributing factor that leads to neurotoxicity.*

Key words: *schizophrenia - voxel-based morphometry - grey matter volume - psychotic episode - neurotoxic hypothesis*

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INTRODUCTION

The neurodegenerative theory suggests that the main cause of schizophrenia is a neurodegenerative process (Kraepelin et al. 1919, Lieberman 1999), primarily resulting in cortical frontal and prefrontal grey matter (GM) atrophy as well as reduction of pyramidal cells number in the thalamocortical and corticocortical tracts followed by white matter (WM) decrease, probably occurring due to axonal atrophy, genetic disorder of myelin or unrecognized infections (Silva et al. 2019). The before mentioned changes are accompanied by ventricular system enlargement, particularly the lateral ventricles, and increased cerebrospinal fluid (CSF) volume (Keshavan et al. 1998, Lawrie et al. 2002, Horga et al. 2011, Sayo et al. 2012).

The NH is based on the Kraepelinian idea of connection between clinical deterioration and brain damage (Kraepelin et al. 1919, DeLisi 2008). Further on, Wyatt investigated effects of neuroleptic treatment on the natural course of schizophrenia, and suggested that psychosis is biologically toxic resulting with brain tissue degradation with every PE (Wyatt 1991). Neurotoxicity results from repeated exposure to neurochemical stressors (Lieberman et al. 1997), which are released during PE, and by stress-related hormones that induce functional and structural brain abnormalities leading to neurodegeneration (Wood et al. 2009).The NH was further complemented with findings that the duration of untreated psychosis (DUP) could be neurotoxic and a predictor of poorer disease outcome (Lieberman et al. 1993). DUP may induce neuronal excitotoxic damage, therefore it can be considered a possible explanation for neurotoxicity (Goldberg et al. 2009, McKenzie 2014) DUP can also be understood as one of the neurotoxic insults and has been associated with GMV reduction (Olney & Farber 1995, Seok Jeong et al. 2005, Gur et al. 1998b).

The clinical course of established schizophrenia is characterized by alternations of PE, remissions and relapses (Kim & Dilip 2008). Mild and moderate GMV reduction was described in SP with first PE (Zipursky et al. 1998, Shenton et al. 2001). During lifetime some SP have one or few PE, while others have numerous, therefore it could be hypothesized that if every PE is considered as a neurotoxic insult, more prominent GMV loss can be expected in SP with multiple PE while less GMV loss can be expected in SP with few PE.

Longitudinal MRI studies reported progressive cortical GMV reduction over time in SP (Vita et al. 2012). Schizophrenia shows progression of GMV abnormalities related to DD, where GMV reduction began in the thalami, progressed to the frontal lobes, and then to the temporal and occipital cortices as well and the cerebellum (Jiang et al. 2018). Greater GMV reduction was associated with longer DD and with usage of higher doses of antipsychotic medication (Shenton et al. 2001).

The aim of this study was to test the hypothesis that SP with multiple PE have greater GMV reduction compared to SP with fewer PE, regardless of DD. To the best of this author's knowledge, there are no known publications showing the relationship between the number of PE and GMV changes in SP.

SUBJECTS AND METHODS

Subjects

We included 106 adults diagnosed with schizophrenia according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (Organization 2004) and Diagnostic and Statistical Manual of Mental Disorders-IV (1994). The SP were recruited from the Psychiatric Clinic, Clinical Hospital Centre Rijeka, Croatia. Clinical assessment was performed by a specially trained psychiatrist (G. R.) who also measured illness severity using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987).

The whole group of 106 SP with schizophrenia was divided into two similar groups according to the number of PE: a group of 61 SP with up to 3 PE (SCHG-1) and a group of 45 SP with 4 or more PE (SCHG-2). Further on, SCHG-1 was subdivided regarding DD: a group of 30 SP with DD up to 3 years (SCHG-1A) and a group of 31 SP with DD of 4 years and longer (SCHG-1B) shown in Figure 1. SCHG-2 has not been divided in subgroups, since the number of SP in the group was too small, thus impairing statistical analysis. The HCG consisted of 63 adult participants, without previous history of psychiatric or neurological illness or head trauma. After a comprehensive description of the study to the subjects, written informed consent was obtained from all participants. The demographic data for all participants is shown in Table 1.

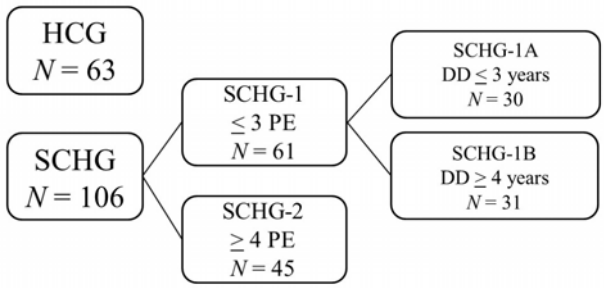

Figure 1. Subject classification: HCG and SP groups (SCHG-1, SCHG-2, SCHG-1A and SCHG-1B) according to the number of PE and DD

Table 1. Demographic and clinical characteristics of healthy control group (HCG) and schizophrenia patients groups (SCHG)

	HCG (*N*=63)	SCHG-1 (*N*=61)	SCHG-2 (*N*=45)	Statistical analysis[a] *t*, *Z* or χ^2	*p*	SCHG-1A (*N*=30)	SCHG-1B (*N*=31)	Statistical analysis[b] *F* or χ^2	*p*
Age (years)	33 (29, 40)	30.3±11.6	43.2±10.6	32.04	<0.0001*	22.6±6.9	37.7±10.4	60.82	<0.0001**
Gender (male/female)	30/33	36/25	28/17	2.71	0.257	18/12	18/13	2.74	0.434
Dominant hand (right/ left/ambidextrous)	59/2/2	54/6/1	44/1/0	3.45	0.178	27/3/0	27/3/1	3.64	0.302
Age of DO (years)		23.1±6.8	26.2±6.9	2.24	0.027	22.1±7.1	24.2±6.4	3.22	0.044***
DD (years)		5 (0, 12)	17.0±8.5	5.31	<0.0001	0 (0, 1)	12 (9, 16)	65.71	<0.0001[+]
Number of PE		2 (1, 2)	7 (5, 12)	8.77	<0.0001	1 (1, 2)	2 (2, 3)	84.08	<0.0001[++]
PANSS general		50.1±8.2	51.8±7.9	1.14	0.260	50.2±8.9	49.9±7.5	0.64	0.526

Values represent frequency of data; mean ± standard deviation for normally distributed data; and median with interquartile range for data that are not normally distributed.

HCG - healthy control group; SCHG-1, SCHG-2, SCHG-1A, SCHG-1B - schizophrenia patients groups defined as shown in Figure 1; DO – disease onset; DD – disease duration; PE – psychotic episodes; PANSS – Positive and Negative Syndrome Scale;

[a]HCG, SCHG-1 and SCHG-2; continuous variables were analysed by *t*- test, Mann-Whitney test or Kruskal-Wallis test (with multiple comparisons of mean ranks as a *post hoc* analysis) and categorical data by χ^2 test;

**post hoc* analysis proved that there is statistically significant difference in age between SCHG-2 and other two groups (p=0.001);

[b]HCG, SCHG-1A, SCHG-1B and SCHG-2; continuous variables were analysed by ANOVA (with Tukey HSD test as a *post hoc* test) or Kruskal-Wallis test (with multiple comparisons of mean ranks as a *post hoc* analysis) and categorical data by χ^2 test;

***post hoc* analysis proved that there are statistically significant differences in age between SCHG-1A and all the other groups (p<0.0001), as well as between HCG and SCHG-2 (p<0.003);

****post hoc* analysis proved that there is significant difference in the age of DO between SCHG-1A and SCHG-2 (p=0.035);

[+]*post hoc* analysis proved that there are statistically significant differences in DD between SCHG-1A and all the other groups (p<0.0001);

[++]*post hoc* analysis proved that there are statistically significant differences in number of PE between SCHG-2 and all the other groups (p=0.0001)

All participants gave their signed written informed consent and patients anonymity were preserved. The Ethical Committee of Clinical Hospital Centre Rijeka approved the study, which was performed in accordance with the ethical principles laid down in the seventh and current edition (2013) of the Declaration of Helsinki.

MRI data imaging and processing

Brain imaging was acquired on a single 1.5 T Magnetom Avanto Siemens (Erlangen, Germany) using a 32-channel head coil and a tilted T1-weighted coronal 3D magnetization prepared rapid acquisition gradient echo sequence (MP-RAGE: TR 2400 ms; TE 3.61 ms; flip angle 8°; FoV 240 x 240 mm; matrix 192 x 192; two acquisitions). This sequence produced 160 contiguous images (slice thickness 1.2 mm), sagittal orientation.

The whole-brain images pre-processing and data voxel-based morphometry (VBM) analysis was done with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) using the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB 9.0 (The MathWorks, Natick, MA, U.S.A.). After segmentation into GM, white matter (WM) and CSF, the GM and WM segments of all subjects were normalized to create an average anatomical template. DARTEL registration of the GM and WM segments for all the subjects was performed on the template to create individual deformation fields (IDF). The IDF of each subject was used to nonlinearly spatially register the GM segments on the template. Finally, the modulated normalized nonlinear GM segments were smoothed by an 8-mm full-width at half-maximum Gaussian kernel.

Statistical analysis

Group differences in demographic and clinical characteristics were assessed with Statistica 12 (StatSoft Inc., USA). Categorical variables were tested through χ^2 test, while continuous data was first tested for normality by Kolmogorov-Smirnov test. The descriptive statistics for data that are normally distributed are presented with arithmetic mean and standard deviation, while data that do not follow normal distribution are presented with the median and interquartile range shown in Table 1. The significance of differences between two groups of normally distributed data was tested by *t*-test for independent data, while for testing the difference of three and more groups of normally distributed data analyses of variance (ANOVA) and Tukey honestly significant difference test for *post hoc* analysis were used. In case of two groups of data that are not normally distributed, the Mann-Whitney test was applied, and for comparison between three and more groups Kruskal-Wallis test was used as well as multiple comparisons of mean ranks for *post hoc* analysis. The $p<0.05$ value was selected for the level of statistical significance.

To detect regional GMV differences between the groups we used VBM toolbox (http://dbm.neuro.uni-jena.de/vbm) in SPM8 (https://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Age and sex were retained as nuisance variables, and an image threshold of 0.2 was used. During the analysis of clinical data, we observed group differences in the age of disease onset (DO) and DD, so those variables were also used as covariates in all comparisons that included SCHG-1 and SCHG-2. In the same manner, the age of DO and number of PE were used as covariates in all comparisons concerning SCHG-1A and SCHG-1B. Cluster level was set at $k\geq20$ voxels for the whole brain analysis. All analyses were performed at $p<0.05$ significance level with family wise error as a correction for multiple comparisons. Coordinates of significant clusters were converted from Montreal Neurological Institute space to Talairach space using GingerALE (https://www.brainmap.org/ale/). Talairach labels for significant clusters were generated by Talairach Client using a nearest GM search (http://www.talairach.org/client.html). Results were visualized using xjView toolbox (http://www.alivelearn.net/xjview).

RESULTS

Demographic and clinical characteristics

SCHG-2 were older than subjects in both HCG and SCHG-1. SCHG-1 had DO at younger age, shorter DD and fewer PE than SCHG-2 subjects. Further analyses proved that SCHG-1A is the youngest of all examined groups and has shorter DD than SP in SCHG-1B and SCHG-2. Also, SCHG-1A had earlier age of DO than SCHG-2. Both SCHG-1A and SCHG-1B had less PE than SCHG-2. There was no statistically significant difference in the PANSS (general) score between the investigated groups.

Voxel-based morphometry: between group analysis

There were no detectable statistically significant GMV differences when subgroups SCHG-1, SCHG-2, SCHG-1A and SCHG-1B were compared with each other.

A comparison between HCG and SCHG-1 revealed decreased GMV in the right precentral gyrus, right insula and left claustrum in SCHG-1 shown in Table 2 and Figure 2. Right transversal temporal gyrus was the only detected region with statistically significant GMV difference in the HCG and SCHG-1A comparison. Analysis of HCG relative to SCHG-1B resulted in statistically significant GMV differences in right precentral gyrus and right claustrum shown in Table 2. An increased number of brain regions with statistically significant GMV differences were detected by comparison of HCG and SCHG-2: left medial frontal gyrus, left middle frontal gyrus, left medial frontal gyrus, right superior frontal gyrus, left inferior frontal gyrus, right insula, left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, left superior temporal gyrus, left anterior cingulate gyrus, left claustrum, right culmen and left and right declive shown in Table 2 and Figure 3.

Table 2. Results of VBM analyses of GMV differences between HCG and SP divided according to Figure 1

Anatomical region	Number of voxels in cluster	Statistics		Coordinates of voxel with maximal statistical significance (Talairach)		
	k	*t*	*p*	*x*	*y*	*z*
HCG vs. SCHG-1						
Frontal Right, *Precentral gyrus, BD 6*	305	5.96	<0.0001	47.51	-9.27	6.91
Sub-lobar Right, *Insula, BD 13*	502	5.72	0.001	30.88	14.31	11.56
Sub-lobar, Left, *Claustrum*	28	4.83	0.027	-31.64	8.79	12.68
HCG vs. SCHG-1A						
Temporal Right, *Transversal temporal gyrus, BD 41*	117	5.80	<0.0001	48.78	-21.11	12.56
HCG vs. SCHG-1B						
Frontal Right, *Precentral gyrus, BD 6*	43	5.26	0.005	46.12	-7.86	7.02
Sub-lobar Right, *Claustrum*	63	4.81	0.029	28.09	15.60	12.99
HCG vs. SCHG-2						
Limbic Left, *Anterior cingulate, BD 32*	508	5.78	0.001	0.62	34.34	-4.62
Posterior Lobe Left Cerebellum, *Declive*	255	5.48	0.002	-23.21	-61.83	-15.49
Posterior Lobe Right Cerebellum, *Declive*	110	5.48	0.002	22.60	-66.13	-16.47
Frontal Left, *Middle frontal gyrus, BD 8*	34	5.45	0.002	-25.13	20.59	50.4
Limbic Left, *Anterior cingulate, BD 32*	107	5.29	0.004	0.23	34.26	25.9
Temporal Right, *Superior temporal gyrus, BD 22*	136	5.26	0.005	55.80	-9.57	9.72
Frontal Left, *Medial frontal gyrus, BD 10*	49	5.24	0.005	0.61	53.51	1.25
Sub-lobar Right, *Insula, BD 13*	114	5.19	0.006	32.39	22.08	4.21
Temporal Right, *Middle temporal gyrus, BD 22*	37	5.18	0.007	54.58	-12.45	-4.09
Anterior Lobe Right Cerebellum, *Culmen*	43	5.16	0.007	21.22	-49.69	-12.23
Temporal Left, *Superior temporal gyrus, BD 22*	27	5.15	0.008	-52.46	-10.28	6.47
Sub-lobar Left, *Claustrum*	158	5.14	0.008	-31.64	7.39	12.55
Frontal Left, *Medial frontal gyrus, BD 6*	28	5.04	0.012	-18.31	-11.84	50.14
Temporal Left, *Middle temporal gyrus, BD 21*	20	5.01	0.013	-55.14	-21.92	-4.14
Frontal Right, *Superior frontal gyrus, BD 10*	29	4.84	0.026	26.75	48.88	18.82
Frontal Left, *Inferior frontal gyrus*	20	4.79	0.031	-35.52	42.39	0.94

HCG – healthy controls group; SP – schizophrenia patients; SCHG-1– SP group with up to 3 episodes; SCHG-1A – SP with up to 3 episodes and DD up to 3 years; SCHG-1B – SP with up to 3 PE and DD longer than 4 years; SCHG-2 – SP with 4 or more PE

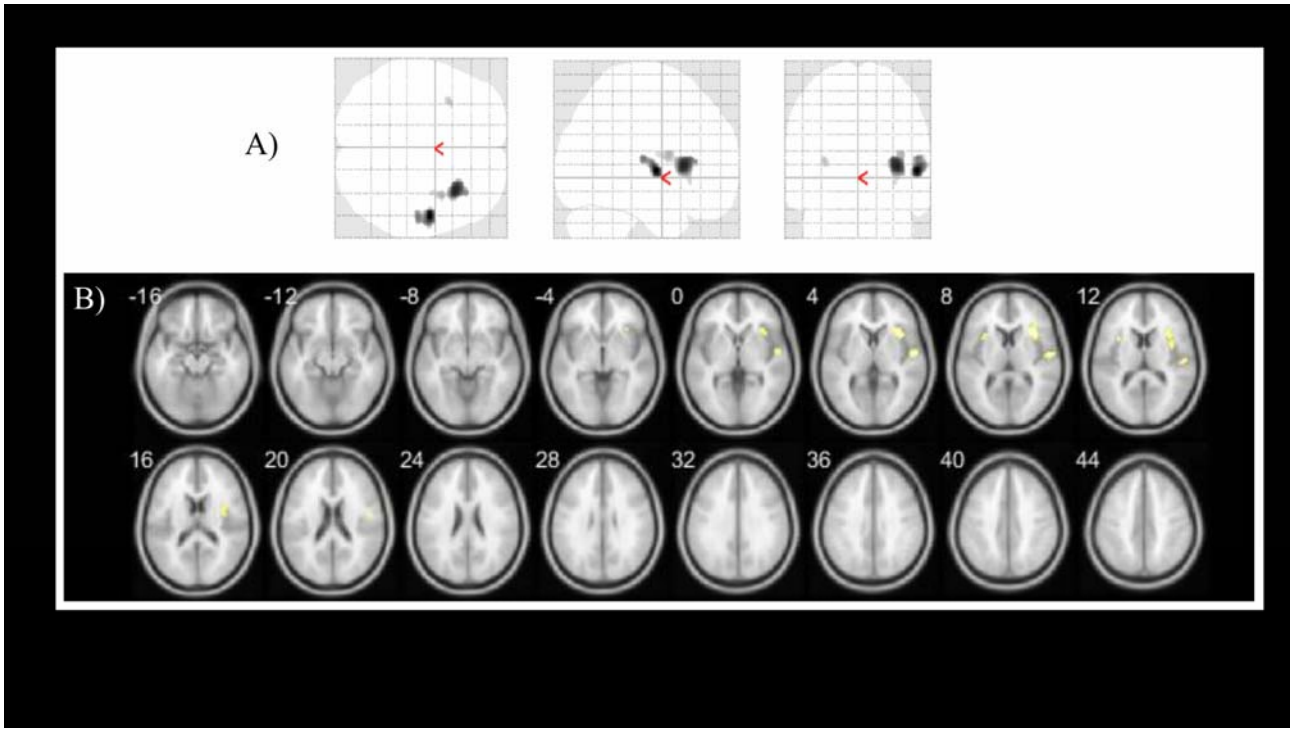

Figure 2. Results of GMV of analysis between HCG and SCHG-1. The yellow-coloured areas indicate brain regions with significantly reduced GMV relative to HCG. The statistical threshold was set at p<0.05 FWE corrected; minimum cluster size = 20. (A) glass view, (B) slice view

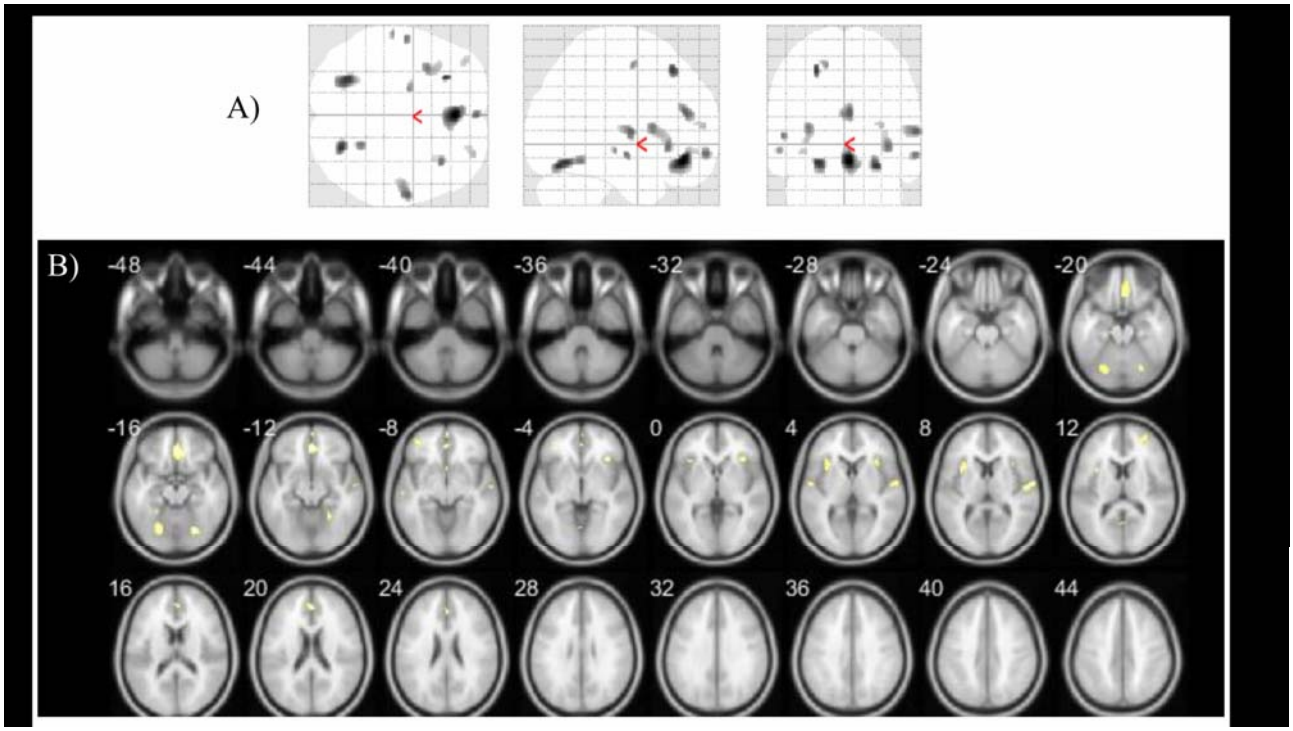

Figure 3. Results of GMV of analysis between HCG and SCHG-2. The yellow-coloured areas indicate brain regions with significantly reduced GMV relative to HCG. The statistical threshold was set at $p < 0.05$ FWE corrected; minimum cluster size = 20. (A) glass view, (B) slice view

DISCUSSION

Our study analyzed the possible influence of the number of PE on GMV in SP. When SP were divided into subgroups according to the number of PE and compared to HCG the findings demonstrated that the number, extension and distribution of affected regions differ. SCHG-1 had only few reduced GMV regions, while SCHG-2 had many regions with reduced GMV. The only common anatomical regions showing GMV reduction in SCHG-1 and SCHG-2 are insula and claustrum. Insular changes contribute to many sensory deficits found in schizophrenia (Wylie & Tregellas 2010) and in chronic SP right insular cortex changes were observed (Nesvag et al. 2008). GMV reduction in insula and claustrum might contribute to positive symptoms in schizophrenia (Roiz-Santianez et al. 2010). Considering the fact that insular thinning is present in early phases of schizophrenia and that it is independent of intervening variables, there is a possibility that changes in insula might be considered as a biological marker for schizophrenia (Shah et al. 2017).

Primary regions of GMV abnormalities in schizophrenia are gyrus rectus, superior temporal gyrus, left hippocampal cortex and insular cortex (Shah et al. 2017). Our study also revealed abnormalities in these regions in SCHG-2, but not SCHG-1. In addition to the above-mentioned regions the most affected brain region in SCHG-2 is the anterior cingulate cortex. Abnormalities in this region are related with cognitive deficits in schizophrenia (Szeszko et al. 2000, McGuire et al. 1998), and thinning of the anterior segment of cingulate cortex is reported to be connected with illness severity and DD (Wang et al. 2007).

Decreased GMV in the cerebellum is associated with a decline in dynamic functional connectivity between the cerebellum and the frontoparietal network in SP (He & Luo 2019). Reduced GMV in vermis and cerebellar tonsils were found in SP with cognitive deficits in first PE (Wang et al. 2017). In our study only SCHG-2 had cerebellar GMV reduction. On the contrary, an influence of number of PE on cerebellar GMV reduction was not observed in recent studies (Yeganeh-Doost et al. 2011, Moberget et al. 2018).

More prominent GMV changes were found when comparing HCG with SCHG-2 in relation to the comparison between HCG and SCHG-1, regardless of DD, which could be suggestive of progressive GMV loss related to the number of PE. This finding may represent the confirmation of NH of schizophrenia; therefore PE could be considered a neurochemical stressor (Lieberman et al. 1997).

Lately, a staging model for schizophrenia has been proposed (Agius et al. 2010, Wood et al. 2011). McGorry`s recognized eight stages of illness and observed GMV reduction in frontal cortex, superior temporal lobe and corpus callosum in the early phase of schizophrenia that progressed as DD increased (McGorry et al. 2010). Many authors found that longer DD and progressive brain changes in chronic schizophrenia are associated with GMV reductions in superior temporal gyrus and in frontal cortex (Chan et al. 2009, DeLisi et al. 2004, Gur et al. 1998a, Mathalon et al. 2001, van Haren et al. 2008, van Haren et al. 2007).

Both SCHG-1 subgroups, SCHG-1A and SCHG-1B, regardless of DD had only one or two regions respectively with GMV reduction when compared to HCG which implicates that the number of PE plays an important role, possibly even more important than DD. Our study did not reveal any GMV difference when schizophrenia groups and subgroups were compared with each other. This might be due to heterogeneity of the factors responsible for neurotoxicity among the groups as well as specific factors for each SP.

Length of DUP is associated with neurotoxicity (Marshall et al. 2005, Perkins et al. 2005), where longer DUP leads to worse cognitive deterioration (Rund 2014). Potential mechanism of neurotoxicity in DUP is dopaminergic hyperactivity which can induce neuronal apoptosis during PE (Crespo-Facorro et al. 2007, Simantov et al. 1996, Anderson et al. 2014). Sometimes, it is hard to determine the exact length of DUP because the compliance of SP is variable (Anderson et al. 2014, Malla et al. 2002). DUP was not observed in our study.

Previously widely used conventional antipsychotics such as haloperidol have been often producing extrapyramidal side effects resulting in neurotoxicity (Ukai et al. 2004), necrosis and apoptosis (Behl et al. 1995, Noh et al. 2000). On the contrary, clinical studies showed advantages of atypical antipsychotics, resulting in neuroprotection, neurotrophins production and neurogenesis (Wakade et al. 2002, He et al. 2009). Medication adherence is also variable in psychiatric patients, including SP. It can vary from complete nonadherence to partial adherence and complete adherence (Svestka & Bitter 2007, Higashi et al. 2013). Nonadherence to medication has an impact on DD, length of PE, on relapses, rehospitalization and consequently on neurotoxicity (Leucht & Heres 2006). Our SP were treated with both conventional and atypical antipsychotics, and medication usage was not observed in this study. Therefore, a major limitation to our study is that we did not observe all the contributing factors which can lead to neurotoxicity.

On the other hand, the nonexistence of GMV differences when schizophrenia groups and subgroups were compared with each other could be explained by how the groups were formed. Our grouping aimed for a similar number of SP in each category, therefore it could be postulated that future studies could detect GMV differences between SP if other criteria for grouping according to the number of PE would be applied, while keeping the groups large enough for comparison.

CONCLUSIONS

We found that the number of PE results in neurotoxicity and has more impact on GMV changes than DD, but the number of PE is not the only factor leading to neurotoxicity. Therefore, further studies should include SP groups with more homogenous distribution of factors responsible for neurotoxicity.

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Conflict of interest: None to declare.

Contribution of individual authors:

Antonija Ružić Baršić: writing original draft, formal analysis, investigation, conceptualization.

Gordana Rubeša: writing – review and editing, resources, supervision, conceptualization.

Diana Mance: validation, writing original draft, software, methodology.

Damir Miletić: supervision, writing - review and editing.

Lea Gudelj: resources, writing - review and editing.

Ronald Antulov: writing - review and editing, software, methodology, supervision.

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