Review of ‘A systematic examination of brain volumetric abnormalities in recent-onset schizophrenia using voxel-based, surface-based and region-of-interest-based morphometric analyses’

In this study the authors’ aim: “to systematically examine brain morphometry in patients with recent-onset schizophrenia to find out if there are significant whole-brain or regional volumetric differences detectable at the appropriate significance threshold, after attempting to control for various confounding factors that could impact brain volumes”.

Although the rationale is sound, the issue has recently been extensively reviewed (Haijima SV et al. Schizophr Bull 2012), and volume reductions in caudate and thalamus may be expected. At least the implications of the findings in this reference should be addressed.

Some suggestions to improve the manuscript are listed below.

Order and issues addressed are based on:
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A major concern with the present data is the external validity of the clinical data. It is stated that: “All patients had predominant positive symptoms” (p. 17). However, inspection of Table 1 reveals that the mean PANSS positive score was “14.60 (5.86) 2-27”. These figures equals a mean PANSS positive score of around 2 per item. Clinically, this translates into an uncertainty of the presence of a symptom.

If the latter figures in PANSS positive cell (“2-27”) indicates the range this is also problematic, since the minimal PANSS positive score is 7. Similar problems are evident from the PANSS Negative, ‘Global(?)’ (which must be corrected to ‘General’), and Total PANSS scores.

In conclusion, from the data presented these subjects appear highly selected and clinically very stable. A concern is therefore, that this low level of symptomatology (at least in some cases) may have resulted in great difficulties in setting a correct clinical diagnosis. The authors argue that diagnoses were confirmed by consensus; however, the data still leaves a clinical concern.
Indeed, associations between brain volumetric measures and psychopathology have been inconsistently reported in the literature. Regardless, the conclusions in the present study may be biased by the fact that these patients apparently did not display as severe psychopathology as what is generally reported in first episode studies.

Please address.

P 7: “Total brain volume (TBV) was significantly lower in patients with schizophrenia (mean=1072.74, s.d.= 117.81) when compared to healthy subjects (mean=1093.16, s.d.= 120.89) using analysis of covariance (ANCOVA), controlling for ICV, gender, age, cumulative neuroleptic exposure and duration of illness (F=5.24, p<0.03) (Figure 1A).”

Inherently, when performing group comparisons, there are some conceptual difficulties with correcting for variables which have not been obtained (or are irrelevant) in both groups. Please address.

Specifically, why correct for duration of illness and neuroleptic exposure, but not for psychopathology?

Please argue for the a priori(?) selection of potentially confounding variables.

Abstract: “However, when socio-demographic and clinical confounding factors were controlled at the sample recruitment and data analyses stages, no significant regional brain morphometric abnormalities emerged at the appropriate statistical thresholds.”

It is implied that putatively ‘random’ regional volumetric differences may be present, in fact this is the main hypothesis in this study. Therefore, it would strengthen this manuscript if the authors would first analyze the data without controlling for “socio-demographic and clinical confounding factors” (to demonstrate that such random volumetric blobs appear). In a next step, the present analyses including the confounding factors could be presented (to demonstrate that the blobs disappear).

P 7: It is stated that: “Medicated patients with ROS (n=24) (mean=1078.72, s.d.=132.45) had significantly lower TBV when compared to HCS (n=45) (mean=1093.16, s.d.=120.89) (F=5.835, p<0.02), while no significant differences in TBV emerged between neuroleptic-naive patients with ROS (n=21) (mean=1065.90, s.d.=101.32) and HCS (n=45) (F=2.538, p<0.12).”

These figures reveal that the naïve patients had numerically lower TBV than medicated patients. Is this difference between patient groups significant? If so, this should be discussed in the context of the hot debate on medication induced brain changes (eg. Ho et al. Arch Gen Psych 2011).

Accordingly, to refine the current analyses one strategy could be to systematically perform separate analyses of drug-naïve vs medication free subjects. This contrast could add knowledge to the potential (and hotly debated) effect of minimal medication exposure on brain structure in recent onset
schizophrenia. Likewise, the data on these two patient groups could be displayed separately in Table 1. This could also save some of the rich supplementary material (Table ST-2)

Methods are well-established, appear well-conducted and well-presented. The authors make extensive examinations of gray matter. However, adding analyses of white matter and CSF (which may also be affected in schizophrenia) may add to the scientific merit of this study. At least is should be discussed if/why this is omitted.

The manuscript is generally well-presented and well-written. No ethical concerns are unattended.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.