Reviewer’s report

Title: A voxel-based morphometric study of regional brain volumes in anorexia and its subtypes

Version: 1 Date: 2 August 2011

Reviewer: Andreas Joos

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Though pseudoatrophy has long been known in Anorexia nervosa (AN), only recently it has become possible to study region specific effects, and whether white or grey matter (WM, GM) is affected. Furthermore differences between the restrictive and bulimic subtypes have not been published.

This study compares sample of 14 AN patients with healthy controls, and samples of seven of the subtypes with each other.

Major Revisions

Before going into further details, I commend on more general issues:

In the Introduction previous studies are lumped together, i.e. region of interest and whole brain studies. I strongly suggest comparing and focusing on recently published whole brain VBM analyses, which have the strong advantage not to focus on regions a priori. The present study should compare findings with four so far published studies, i.e. Castro-Fornieles et al 2009, Joos et al 2010, Boghi et al 2011, Guadio et al 2011). Similarities of regional changes as well as patient characteristics should be discussed and compared (subtypes investigated, adults/adolescents, BMI, lowest-life time BMI etc) as well as similarities and differences which might be due to the technical/statistical approach.

The issue of comparing AN subtypes should include a discussion of these subtypes, i.e theories and concepts about these clinical syndromes and findings in other studies, i.e. neuropsychological, neurobiological, psychodynamic aspects etc in more detail (in particular with respect of the upcoming DSM V..).

Importantly a comparison of samples with seven patients (without any similar previous investigations) should only be viewed as exploratory. Any hypotheses seem clearly too far reaching. Furthermore, the subtypes differ with respect to the lowest life time BDI: This is probably the most important parameter with respect to persisting changes of GM (see in particular, Mühlau et al 2007, also Joos et al 2011). Hence, an exploratory analysis must consider these values as covariates.

The Introduction emphasises correlations of BOLD signals and GM: this is a very important (and complicated, hopefully a focus in future studies of mental disease) issue: As this study does not provide any data in this respect, it is a bit misleading and might be mentioned briefly, only (one sentence, maybe in the
Discussion section).

Specifically:

Introduction:
see above

Methods:
This section should started with “Participants”.

Setting~ MRI data acquisition

Statistical analysis: might be differentiated: VBM (pre) processing + stat anal.

Why Talairach (not really necessary if not recommended by journal style)?
BAMM package should briefly be explained.

(Comparison Controls with subgroups might be done/mentioned (supplemental material)

Covariates : see above when comparing subgroups. Furthermore see papers published 2011 with this respect (Gaudio, Boghi 2011 both).

Explain:
1. Why cluster level and not voxel level, why not both?
2. 0.002 AN vs HC and 0.01 subgroups (What does it exactly mean),
3. “Number of clusters less than one”? (What does it imply precisely)
4. Why not FDE or FWE ?

Correl. + Regr: under statistics section....
And: Why not analyses over the whole brain (like in Joos et al);

Duration of illness link to GM: it is well established that this does not play a major role in the context of starvation in AN, i.e in GM reduction (see papers above in ill patinets, as well as Mühlau et al) - however it might play a role in the context of neuropsychology, e.g. control behaviour, which this paper alludes to. (It might be mentioned as a post hoc analysis mentioned briefly)

Why not correlate shape + weight concern with GM in particular of posterior (temporoparoietal regions) or do a whole brain analysis (in particular with regards to results of Guadio et al , Boghi et al and Joos et al, finding posterior brain GM reduction and correlations with shape concern/drive for thinness, or Suchan et al 2010)

Results:
binge/purge: monthly bases. How often? Only once?
Voxelwise: AN vs HC: 1st sentence not necessary

Was the EBA also affected in their sample (less GM, see e.g. Suchan et al. 2010)?

RAN vs BPAN: 1st sentence not necessary
Covariate lowest life time BMI! (see above)

Discussion:
The missing difference of WM, GM + CSF compared to controls is unusual and deserves discussion in detail (including VBM studies as well as other earlier reports). (WM is even increased in AN though not significantly)

Regional differences must be discussed within the context of the mentioned other four VBM studies.

The largest area of GM reduction concerned the cerebellum: compare with Boghi et al 2011.

The increase of DLPFC volume is of great interest and new - compared with the other studies. This should be a focus - though it is already discussed. This might be done in more detail

The comparison of subgroups is exploratory with very small samples and should be discussed briefly within this context.

PS: From a psychopathological view point one might expect increased DLPFC GM in RAN compared to BPAN, which is not the case. This should be discussed.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'