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Why Ruminators Won't Stop

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Running Title: Why Ruminators Won't Stop

Why Ruminators Won't Stop: The Structural And Resting State Correlates Of Rumination And Its Relation To Depression.

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Abstract

Background: Rumination is a good predictor of major depression. The current study explores the structural and functional neural correlates of rumination.

Methods: To explore structural correlates of rumination (RRS, Treynor et al. 2003) we used voxel-based morphometry. We relate these correlates of rumination to concurrence of grey matter reductions in depressed patients by means of a quantitative meta-analysis on 16 VBM studies. Resting state data was used to compute maps of the amplitude of low frequency fluctuations.

Results: Rumination correlated negatively with grey matter volume in bilateral inferior frontal gyrus (IFG), left anterior cingulate cortex (ACC), and bilateral mid cingulate cortex. The volume reductions were within proximity of grey matter reductions identified in the meta-analysis on depressed patients in bilateral IFG and ACC. Moreover reductions in resting state activity were overlapping with volume reductions correlated with in ACC and right IFG.

Limitations: The participants were all healthy control subjects. Future research is needed to explore the neural correlates of rumination in major depression.

Conclusions: The results show that rumination is associated with volume and resting state reductions in brain areas that have been related to cognitive control process of inhibition and thought suppression. We conclude that rumination qualifies not only as a behavioural predictor of major depression but goes along with neuroanatomical abnormalities that are similar to those identified for depression.

Introduction

Self-reflection lies at the heart of human nature. It involves focussing on one's own thoughts, feelings and experiences. Recently research has been concerned with its rather maladaptive form: rumination. Rumination has been defined as a recurrent series of thoughts unified by a common theme (Martin and Tesser, 1996). Moreover the process of thinking has been described as directed to the causes and consequences of one's negative feelings and problems rather than on the specific content of thought (Nolen-Hoeksema, Wisco and Lyubormirsky, 2008). Studies have shown that rumination is consistently related to depressive symptoms (Mor and Winquist, 2002). Moreover, prospective longitudinal studies have shown that people who engage in rumination when distressed are more likely to develop depressive episodes (Nolan, Roberts and Gotlib, 1998; Roberts, Gilboa and Gotlib, 1998, Spasojevic and Alloy, 2001). Ruminators experience episodes of depression that are more numerous, severe, and long lasting than those of people with a lower tendency to ruminate (Lyubomirsky and Nolen-Hoeksema, 1993; Nolen-Hoeksema, 1991).

Up to now the neural correlates of rumination have not been excessively explored. The few studies that have been undertaken focused on task related functional correlates of rumination. Candidate brain regions that have been suggested to be associated with excessive self-referential thinking and rumination are the lateral prefrontal cortex (Hooker et al., 2010; Kross et al., 2009; Putnam and McSweeney, 2008), medial prefrontal cortex including anterior cingulate cortex (ACC, Denson et al., 2009; Johnson et al., 2009), posterior cingulate cortex (Andersen et al., 2009; Johnson et al., 2009) and amygdala (Canli et al., 2006; Ray et al.,

2005; Siegle et al., 2002). The direction of the association between functional brain activity and rumination seems to be less clear (De Raedt and Koster, 2010).

One may be tempted to group existing evidence on the neural correlates of rumination into two subgroups: one establishing a link between rumination and altered activation in the default mode network (Raichle et al., 2001) including medial prefrontal cortex and posterior cingulate cortex (Christoff et al., 2009; Kühn and Gallinat, in press; Mason et al., 2007; Stawarkzyk, et al., 2011); the other establishing a link between rumination and alterations of the task–related control network comprising brain regions such as lateral prefrontal cortex and parietal cortex (Hooker et al., 2010; Putnam and McSweeney, 2008).

We are not aware of any previous studies focusing on structural or resting state correlates of rumination. In order to fill this gap and to understand whether rumination is characterized by alterations in areas of the default mode network, or in the task-related control network, or potentially both we used voxel-based morphometry (VBM) to assess the structural correlates of rumination in a sample of 36 healthy volunteers. Based on the finding that rumination is predictive of major depression (De Raedt and Koster, 2010; Roberts, Gilboa and Gotlib, 1998; Spasojevic and Allow, 2001) one might expect similar neuroanatomical abnormalities as in major depression. In a multitude of studies depression has been related to volume reductions and neuropathological abnormalities in frontal brain regions (especially in the anterior cingulate and the prefrontal cortex) hippocampus, amygdala and the striatum (Harrison, 2002; Koolschijn et al., 2009). Commonalities between abnormalities associated with rumination in affectively healthy subjects and abnormalities associated with depression would constitute evidence in favour of depressions' structural correlates might also be premorbid vulnerabilities instead of consequences of illness and accompanying medication. To relate the structural correlates of rumination to findings from previous VBM studies on depression we performed a quantitative meta-analysis by means of activation likelihood estimation (ALE) (Eickhoff et al., 2009; Laird et al., 2005) on studies that report reductions in grey matter volume or density related to depression. Moreover we explored functional correlates of rumination in functional resting state data, because resting state constitutes a possibility to

study brain activity under natural conditions due to its stimulus-independence which might be especially fruitful to explore tendencies to ruminate.

Method

Participants

38 healthy volunteers recruited from a database at Ghent University of healthy participants took part on the basis of informed written consent, with ethical committee approval of the University hospital Ghent and according to the Declaration of Helsinki. No subject had a history of neurological, major medical, or psychiatric disorder. The participants (28 women and 10 men) had a mean age of 21.3 years (ranging from 18 to 32 years) and were all right-handed as assessed by a handedness questionnaire (Oldfield, 1971). We excluded two participants because they were statistical outliers on the BDI measure with scores of 23 and 25, respectively, indicating moderate depression (possible maximum score 63).

Scanning Procedure

Images were collected with a 3T Magnetom Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) using an 8-channel radiofrequency head coil. First, high-resolution anatomical images were acquired using a T1-weighted 3D MPRAGE sequence (TR = 1550ms, TE = 2.39ms, TI = 900ms, acquisition matrix = 256 × 256 × 176, sagittal FOV = 220 mm, flip angle = 9º, voxel size = 0.9 × 0.9 × 0.9 mm^3). Whole brain functional images were collected using a T2*-weighted EPI sequence sensitive to BOLD contrast (TR = 2000ms, TE = 35ms, image matrix = 64 × 64, FOV = 224 mm, flip angle = 80º, slice thickness = 3.0 mm, distance factor = 17%, voxel size 3.5 × 3.5 × 3 mm^3, 30 axial slices). 207 image volumes aligned to AC-PC were acquired. During the resting state measurement subjects were instructed to keep their eyes closed and to relax.

Questionnaires

In order to assess the tendency to ruminate we administered Rumination Response Scale (RRS, Treynor, Gonzalez and Nolen-Hoeksema, 2003, in the Dutch translation used by Schoofs, Hermans and Raes, in press) with the subscales reflection and brooding. Moreover we measured depression by means of the Beck Depression Inventory-II (BDI-II; Beck, Steer and Brown, 1996). Emotion regulation was assessed by means of the Emotion-Regulation Questionnaire (ERQ, Gross and John, 2003) with the subscales reappraisal and emotion suppression. For all questionnaires, higher scores are indicative of respectively, more rumination, depressive symptoms, relatively more use of a specific type of emotion regulation style.

Voxel-based morphometry analysis

All anatomical data were processed with VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm) with the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm). The toolbox used segmentation algorithm from SPM5 and the extension of Hidden Markov Random Field approach. It has been demonstrated to be superior to previous SPM versions (Ashburner and Friston, 2005). During pre-processing a modulation was performed. This is necessary in order to preserve the volume of grey matter within a voxel since the regular spatial normalisation expands and contracts brain regions. Modulation involves scaling by the amount of contraction, so that the total amount of grey matter in the modulated brain matter remains the same as it would be in the original images. This is achieved by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, an analysis of modulated data tests for regional differences in the absolute amount (volume) of grey matter. Finally we smoothed the images with a 12 mm FWHM kernel.

Then statistical analysis was carried out by means of voxel-wise correlation with either the total rumination score of each participant (controlling for age, sex, total brain volume). A height threshold of $p < 0.001$ and an extent threshold of 100 voxel was applied to the *t* maps to detect local changes in brain volume. In order to correct for multiple comparison we performed a small volume correction defining the resting state results as a priori regions of

interest for the VBM analysis. These results are reported applying family-wise error correction ($p < 0.05$).

Resting state analysis

The first 10 volumes were discarded to allow the magnetisation to approach a dynamic equilibrium, and for the subjects to get used to the scanner noise. Part of the data pre-processing, including slice timing, head motion correction (a least squares approach and a 6-parameter spatial transformation) and spatial normalization to the Montreal Neurological Institute (MNI) template (resampling voxel size of 3mm × 3mm × 3mm), were conducted using the SPM5 and Data Processing Assistant for Resting-State fMRI (DPARSF, Chao-Gan and Yu-Feng, 2010). A spatial filter of 4 mm FWHM (full-width at half maximum) was used. Participants showing head motion above 3.0mm of maximal translation (in any direction of *x*, *y* or *z*) and 1.0° of maximal rotation throughout the course of scanning would have been excluded.

After pre-processing, linear trends were removed. Then the fMRI data were temporally band-pass filtered (0.01 - 0.08 Hz) to reduce the very low-frequency drift and high-frequency respiratory and cardiac noise (Biswal et al., 1995). ALFF analysis (Yang et al., 2007; Zang et al., 2007) was performed using DPARSF (Chao-Gan and Yu-Feng, 2010). The time series for each voxel was transformed to the frequency domain using fast Fourier transform (FFT) and the power spectrum was obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component in the original time series in time domain, the power spectrum obtained by FFT was square rooted and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root constitutes what has been called the ALFF (Zang et al., 2007). The ALFF of each voxel was divided by the individual global mean of ALFF within a brain-mask, which was obtained by removing the tissues outside the brain using software MRIcro (by Chris Rorden, http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). On the resulting maps a

whole brain correlation with the total rumination score was computed. A height threshold of $p < 0.001$ and an extent threshold of 10 voxels was applied to the *t* maps. In order to explore resting-state correlates controlling for the influence of local grey matter volume differences we used the Biological Parametric Mapping Toolbox (Casanova et al., 2007) in which the grey matter volume maps of each subjects were used as a covariate. The resulting maps were thresholded with $p < 0.001$ and an extent threshold of 5 voxels.

ALE Meta-Analysis on structural correlates of depression

Studies were selected using a systematic search of peer-reviewed articles published in English until July 2010. We used separate databases (Medline, Pubmed, ISI Web of Knowledge) with the keywords ''voxel-based morphometry'' <OR> "morphometry" <OR> "volumetry" and "depression" <OR> "mood disorder". The reference lists of these selected papers (n=16) were searched for additional studies that fit these criteria. From the papers found we selected studies for our ALE analysis that reported grey matter reductions of depressed patients (n=401) compared to healthy controls (n=434). Only studies of which we were able to obtain either Talairach (Talairach and Tournoux, 1988) or MNI coordinates were included. Moreover only coordinates resulting from analyses that were computed across the whole brain and not restricted using partial coverage, regions of interest or small volume correction were considered. For studies reporting grey matter volume and grey matter density separately, the coordinates of both measures were entered into the analysis. Altogether 178 foci were included (*Table 1*).

The ALE method provides a voxel-based meta-analytic technique for functional neuroimaging data (Eickhoff et al., 2009; Laird et al., 2005). By means of the software Brainmap GingerALE (http://brainmap.org/ale/) statistically significant concordance in the pattern of brain activity among several independent studies was computed. ALE maps were derived based on foci of interest, which comprise statistically significant peak activation locations from multiple studies. Coordinates reported in Talairach were converted to MNI using Matthew Brett's transformation script (Brett et al., 2001; http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m). In the approach taken by ALE, localization

probability distributions for the foci are modelled as the centre of 3-D Gaussian functions, where the Gaussian distributions are summed across the experiments to generate a map of inter-study consistencies that estimate the likelihood of activation for each voxel as determined by the entire set of studies. The false discovery rate (FDR) method was employed to correct for multiple comparisons at a significance threshold of $p < 0.05$ and a cluster threshold of 100.

We consider convergence of the ALE map with the results of the VBM analysis where clusters do not necessarily exactly overlap but are in close proximity within the same brain structure. Clusters are said to converge if they fall within the same anatomically defined region as e.g. inferior frontal gyrus.

Results

The sample of participants had an average total rumination score of 50.67 (*SD* = 15.0) (the possible range of the scale is between 26 and 104) and a Reflection subscale score of 10.06 (*SD* = 3.9) and Brooding subscale score of 10.13 (*SD* = 3.6). On the Beck Depression Inventory (BDI) participants scored on average 5.62 (*SD* = 3.8; possible maximum score 63) indicating absence of depression. On the subscale of reappraisal on the ERQ participants had a score of 29.53 (*SD* = 5.1) (the possible range of the scale is between 6 and 42), on the suppression subscale 12.9 (*SD* = 4.2) (the possible range of the scale is between 4 and 28). Total rumination score and BDI score were positively correlated (Pearson correlation $r(36) = .45$, $p < 0.01$). We found a positive correlation between the reflective pondering subscale of rumination and the reappraisal subscale of the ERQ ($r(36) = .37$, $p < 0.05$). Moreover we found a positive correlation between the Brooding rumination subscale and suppression subscale of the ERQ ($r(36) = .36$, $p < 0.05$).

VBM rumination

Because we were interested in structural correlates of rumination we computed a whole-brain correlation between the total rumination score and grey matter volume controlling for sex, age and total brain volume. We found clusters that show a negative correlation with rumination in

bilateral inferior frontal gyrus (IFG, BA 45), left anterior cingulate cortex (ACC, BA 32) and bilateral mid cingulate cortex (mCC, BA 23/24) (*Figure 1, Table 2*). No significant positive correlates were found. The results are identical when entering depression (BDI) as a nuisance covariate.

Resting state correlates of rumination

We correlated the whole-brain ALFF maps - suggested to reflect the intensity of regional spontaneous brain activity - with the total rumination score. As a result we found clusters of significant negative correlation in right IFG (BA 45), anterior cingulate cortex (ACC, BA 32) and subgACC (extending into medial orbitofrontal cortex, BA 25/11) (*Table 3).* When comparing those brain areas with a lower intensity of regional spontaneous brain activity for higher ruminators with local grey matter volume reductions in high ruminators we find overlap in right IFG and ACC (*Figure 2*). When defining the resting state results as a priori regions of interest for the VBM analysis by means of small volume correction (using a mask of the brain regions associated with rumination in ALFF) the voxels in right IFG and ACC survive family-wise error correction ($p < 0.05$). In order to test whether the resting state correlates that were overlapping with structural correlates were actually causally related to the local grey matter reductions we used the grey matter volume maps of each subjects as a covariate. Indeed the clusters in right IFG and ACC disappeared. Instead we found a negative correlation with the rumination score in a different, more posterior part of the ACC (BA 24; 3, 18, 30) and bilateral subACC (12, 21,-12; -12, 27, -12).

Meta-Analysis on structural correlates of depression

In a quantitative ALE meta-analysis we found significant convergence across studies of brain regions that show decreases in grey matter between depressed and healthy control subjects in bilateral IFG, right ACC, bilateral medial and left superior frontal gyrus, right subgenual anterior cingulate cortex (subgACC), left parahippocampal gyrus and left caudate, left inferior parietal lobe, left cuneus and precuneus, bilateral cerebellum and right precentral gyrus (*Table 4, Figure 3*). Three clusters of convergence were observed in bilateral IFG and ACC in close

proximity of grey matter regions that correlate negatively with rumination scores in healthy subjects and regions identified in the meta-analysis on depressed patients vs. healthy controls (*Figure 4)*.

Discussion

The present study explored structural and resting state correlates of self reported rumination, a thinking style that has been found to be predictive of major depression in affectively healthy subjects. A VBM analysis revealed a negative correlation between grey matter volume and rumination in bilateral IFG (BA 45), left ACC (BA 32) and bilateral mCC (BA 23/24). Moreover we found grey matter reductions in regions identified in the quantitative meta-analysis on depressed patients vs. healthy controls to be in close proximity to grey matter reductions that correlate negatively with rumination scores in healthy subjects in bilateral IFG and ACC.

Resting state (ALFF) correlates of rumination were found in areas overlapping with grey matter volume reductions in ACC and right IFG. The fact that this overlap was absent when controlling for regional grey matter implies that the resting state results in ACC and right IFG can at least partly be explained be the structural reductions. It could suggest that common mechanisms participate in both processes or that a causal relationship exists between atrophy and hypometabolism (Chételat et al., 2008).

Structural and functional correlates of rumination

Regions of grey matter reduction that were correlated negatively with rumination scores, were found in bilateral IFG (BA 45), left ACC (BA 32) and bilateral mCC (BA 23/24). These brain regions, in particular bilateral IFG and left ACC are part of the task-related control network (Corbetta and Shulman, 2002). An additional analysis with SPM8 and DARTEL yielded a cluster in callosal white matter extending into the lateral ventricle that correlated negatively with rumination. Although registration by means DARTEL has been shown to be of high quality (Klein et al., 2009) a finding of a cluster that is clearly in the white matter in an

analysis on grey matter segmentations does not appear to be valid. Therefore we report the results of VBM by means of VBM5. The brain regions identified here have previously been associated with functional studies on rumination. In support of the importance of right IFG and ACC in rumination we found a negative correlation between resting state (ALFF) activity and the rumination score in areas overlapping with the grey matter volume reductions observed by means of VBM. This is yet more supporting evidence for the notion that alterations in the task-related control network are the neural basis underlying rumination.

In line with the present finding a study by Hooker et al. (2010) used brain signal in response to viewing positive, negative and neutral facial expressions of the partner in order to predict whether interpersonal conflict resulted in rumination. They found that lower activity levels in IFG (triangularis) predicted higher rumination. Evidence for problems in control in depression comes from a study on remitted patients that showed less activity of IFG than control participants during viewing of fearful as compared to neutral emotional faces (Thomas et al., 2011). Similarly decreases in task-unrelated resting baseline PFC alpha activity have been associated with higher levels of rumination in individuals suffering from depression (Putnam and McSweeney, 2008). A study exploring cognitive reappraisal found a correlation between interindividually higher levels of rumination and a reduction of prefrontal cortex activation while regulating negative affect (Ray et al., 2005).

Posterior cingulate activity in theta power response in EEG has been associated with rumination in a study by Andersen et al. (2009). In a similar vein Johnson et al. (2009) related individual differences in rumination with the mid cingulate cortex and ventromedial prefrontal cortex.

Contrary to the results presented, previous task-free studies in depression have reported increases in resting state activity in the fronto-median cortex (Kühn and Gallinat, in press). Moreover a positive association between functional connectivity of the fronto-medial cortex and rumination has been shown in depressed patients (Zhu et al., in press). It may therefore be that in depression rumination is associated with an overactivity of the default mode network, whereas in healthy controls rumination is related to a hypoactivation of the task-network consisting of brain regions such as IFG and ACC. Future research should focus on potential

differences between the neural correlates of rumination in healthy controls and depressed patients.

Neural correlates of rumination and its relation to inhibition

On the behavioural level depressive rumination has been associated with an inability to effectively inhibit perseverative tendencies (Whitmer and Banich, 2007; De Lissnyder et al., in press). In a similar line depressed patients have been reported to show an association between reduced inhibition of negative stimulus material that was related to higher levels of rumination and reduced inhibition has been related to more use of suppression strategies in emotion regulation in major depression (Joorman and Gotlib, 2010). Supporting evidence for this association might be seen in the positive correlation of the brooding subscale and suppression in emotion regulation. To summarize more and more studies relate rumination to problems with inhibition on the behavioural level but the studies that have focussed on the neural underpinnings are limited.

Neurally successful inhibition has been associated with the integrity of the ventral prefrontal cortex, in particular the right IFG, the presupplementary motor cortex (preSMA), the ACC and the basal ganglia (for an overview Chambers et al., 2009). In the following we are going to describe the involvement of those brain regions in more detail.

Especially in context of response inhibition the right (but also left) IFG has been implicated in the exertion of control over behaviour that needs to be stopped (Aron et al., 2003). Extending those findings of response inhibition the IFG has lately also been implicated in the suppression of non-emotional and emotional memories (Anderson et al., 2004; Depue, Curran and Banich, 2007). A study by Hamilton and colleagues (2011) has shown an overactivity of the default-mode network in depressed patients that was associated with higher levels of maladaptive rumination. Healthy control participants on the other hand showed increases in right IFG and insular cortex activity at the onset of increases in default mode network activity that is interpreted as an adaptive engagement of the task-related network preventing maladaptive rumination.

The ACC has repeatedly been associated with thought suppression. In a study by Wyland et al. (2003) subjects hat to come up with a personally relevant thought which then had to be suppressed or could be freely thought about. The ACC (as well as the left IFG) was related to getting the salient thought out of the mind (Anderson et al., 2004, Mithell et al., 2007).

To summarize, the brain regions that were found to be structurally as well as functionally negatively correlated with rumination are part of the task-related control network that has been related to inhibition of action and inhibition of thoughts.

Neural correlates of rumination and its relation to major depression

In previous VBM studies comparing patients suffering from major depression with healthy controls reductions of frontal regions (especially in the anterior cingulate and the prefrontal cortex), hippocampus, amygdala and the striatum have been described (Harrison, 2002; Koohlschijn et al., 2009). In our quantitative meta-analysis we find clusters of convergence in bilateral IFG, ACC, bilateral medial and left superior frontal gyrus, subgenual cingulate cortex, left parahippocampal gyrus and left caudate that are in line with these narrative-based meta-analytic studies. Surprisingly we find no convergence in VBM whole-brain studies in amygdala or hippocampus although region of interest based volumetric analysis consistently revealed differences (Hajek et al., 2009; Hamilton, Siemer and Gotlib, 2008).

We conducted the quantitative meta-analysis in order to compare our rumination findings with VBM results on major depression in the literature. Most importantly, this comparison reveals commonalities between abnormalities associated with rumination and depression. We suggest that this is evidence in favour of the notion that the structural correlates of major depression (at least those in IFG and ACC) could be premorbid vulnerabilities instead of consequences of the illness and accompanying medication.

Limitations

Within the scope of the present study we explored the neural correlates of rumination within healthy participants. Future research should focus on the correlates in patients with major depression.

To summarize, the present results associate rumination with grey matter reductions and resting state alterations of affectively healthy participants in right IFG and ACC, brain regions that have been related to inhibition of thoughts and memories. Our results therefore suggest that rumination in healthy participants is rather characterized by an alteration of the task-related control network, than by an alteration of the default-mode network.

Moreover the present findings suggest that rumination not only qualifies as a predictor of major depression but goes along with structural abnormalities that are similar to those identified in major depression.

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Conflict of interest

SK, MAV, RDR report no financial relationships with commercial interests. JG has received research funding from the German Federal Ministry of Education and Research (BMBF 01GS08159), research funding from AstraZeneca, Eli Lilly & Co, Janssen-Cilag, Bristol-Myers Squibb and speaker fees from AstraZeneca, Janssen-Cilag, and Bristol-Myers Squibb. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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The funding sources had no influence in data acquisition, data analysis or data interpretation.

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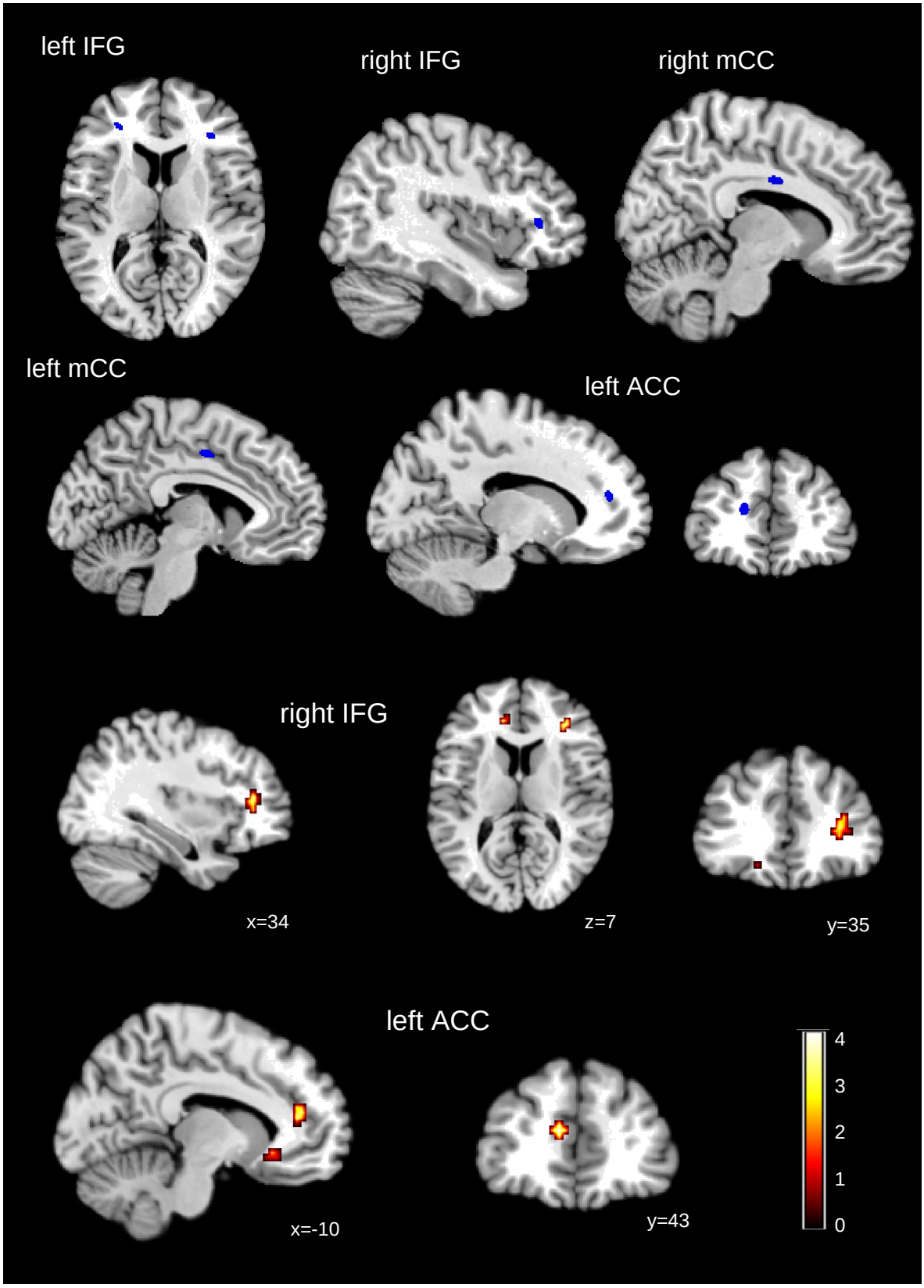
Figure captions

Figure 1: Negative whole-brain correlation of grey matter volume and total rumination score ($p < 0.001$, cluster size > 100). Results are overlayed onto a T1 weighted MNI single subject template (colin27). IFG = inferior frontal gyrus, mCC = mid cingulate cortex, ACC = anterior cingulate cortex.

Figure 2: Negative whole-brain correlation of amplitude of low frequency fluctuations (ALFF) and total rumination score when not controlling for grey matter volume correlates ($p < 0.001$, cluster size > 10, displayed in orange). Results are overlayed onto a T1 weighted MNI single subject template (colin27). ACC = anterior cingulate cortex, IFG = inferior frontal gyrus.

Figure 3: Results of a quantitative meta-analysis on VBM studies comparing grey matter alterations in depressed patients and healthy controls (FDR $p < 0.05$, cluster size > 100). Results are overlayed onto a T1 weighted MNI single subject template (colin27).

Figure 4: Display of overlap and close proximity of brain regions observed in the negative correlation of grey matter volume and rumination (blue), in the negative correlation of resting state amplitude of low frequency fluctuations (ALFF) and rumination (orange) and grey matter abnormalities in major depression assessed by means of a quantitative meta-analysis (dark red).


left IFG
right IFG
right mCC
left mCC
left ACC
right IFG
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z=7
y=35
left ACC
x=-10
y=43
4
3
2
1
0

Figure 1

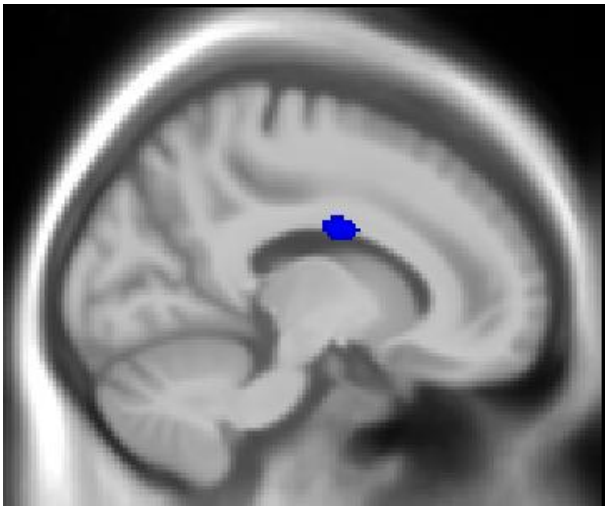

Figure 2

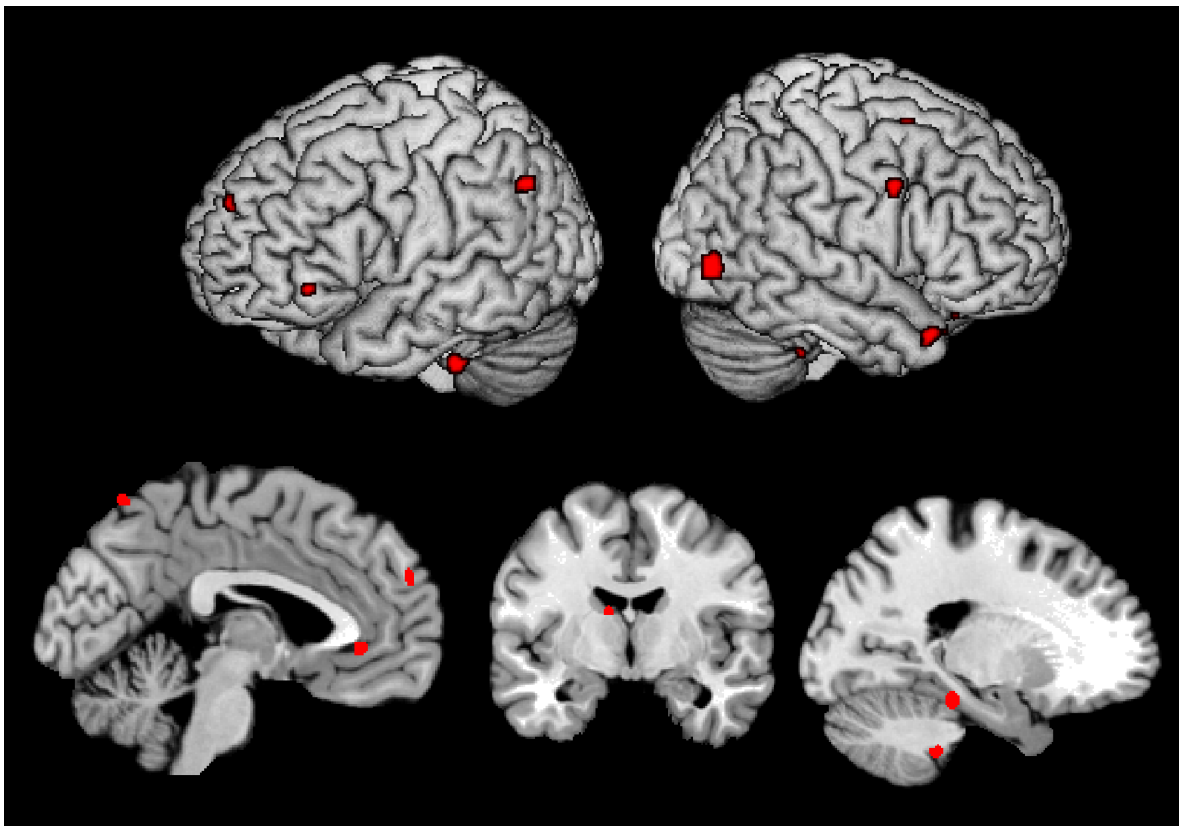

Figure 3

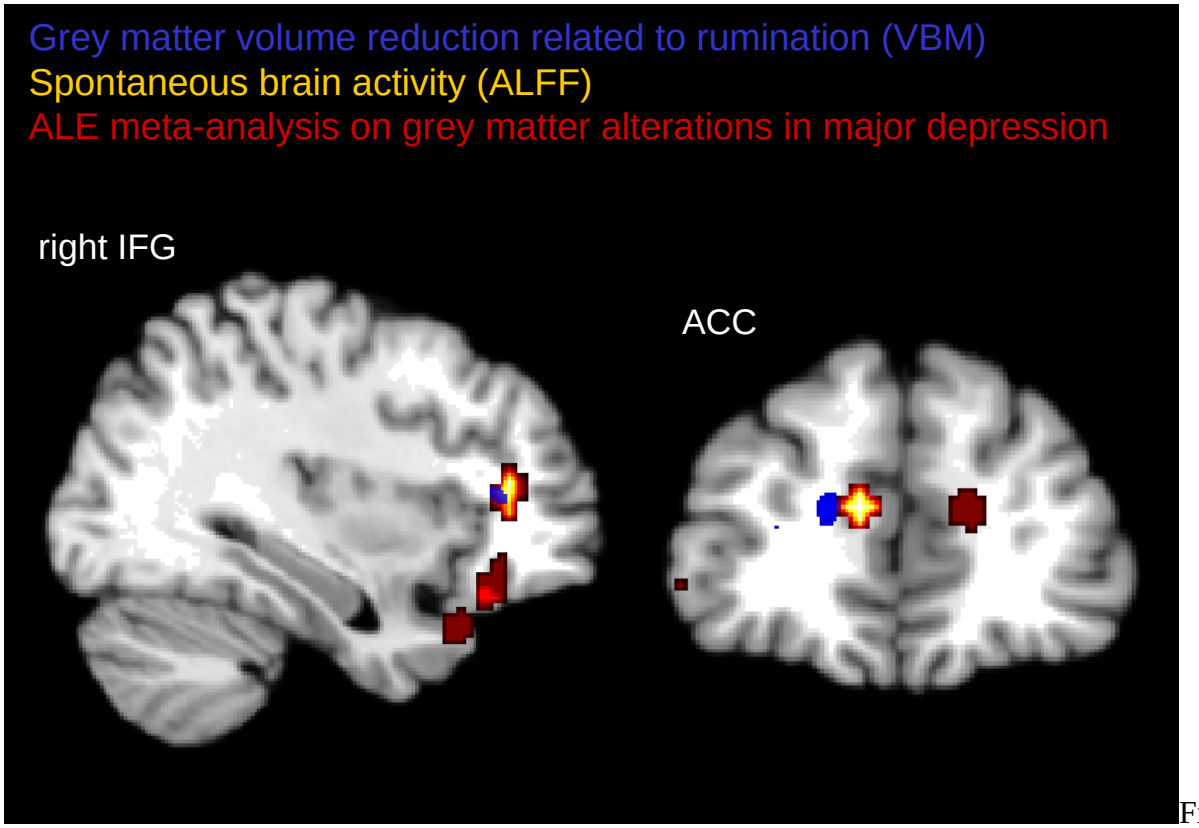
Grey matter volume reduction related to rumination (VBM)
Spontaneous brain activity (ALFF)
ALE meta-analysis on grey matter alterations in major depression
right IFG
ACC

Figure 4