Meta-analysis of resting-state fMRI in depression

generating spatial hypotheses for potential clinical applications

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Information derived from functional magnetic resonance imaging (fMRI) during wakeful rest has been introduced as a candidate diagnostic biomarker in unipolar major depressive disorder (MDD). Multiple reports of resting state fMRI in MDD describe group effects. Such prior knowledge can be adopted to pre-select potentially discriminating features, for example for diagnostic classification models with the aim to improve diagnostic accuracy. Purpose of this analysis was to consolidate spatial information about alterations of spontaneous brain activity in MDD to serve such feature selection and as a secondary aim to improve understanding of disease mechanisms. 32 studies were included in final analyses. Coordinates extracted from the original reports were assigned to two categories based on directionality of findings. Meta-analyses were calculated using the non-additive activation likelihood estimation approach with coordinates organized by subject group to account for non-independent samples. Results were compared with established resting state networks (RSNs) and spatial representations of recently introduced temporally independent functional modes (TFMs) of spontaneous brain activity. Converging evidence revealed a distributed pattern of brain regions with increased or decreased spontaneous activity in MDD. The most distinct finding was hyperactivity/ hyperconnectivity presumably reflecting the interaction of cortical midline structures (posterior default mode network components associated with self-referential processing and the subgenual anterior cingulate cortex) with lateral frontal areas related to externally-directed cognition. One particular TFM seems to better comprehend the findings than classical RSNs. Alterations that can be captured by resting state fMRI show considerable overlap with those identifiable with other neuroimaging modalities though differing in some aspects.

1. Introduction

Mental disorders featuring depression as a predominant symptom and more specifically major depressive disorder (MDD) are important worldwide public health concerns. In recent years significant progress has been achieved regarding the identification of biological correlates and potential neural mechanisms involved in the pathogenesis of

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MDD. These scientific efforts comprise studies of genetic foundations, molecular mechanisms including neurotransmitter systems and structural as well as functional neuroimaging (Kupfer et al., 2012). Thereby candidate neural systems have been identified that support emotion processing, reward seeking, regulate emotion and are therefore presumed to play an important role in MDD. These networks include subcortical as well as cortical (particularly prefrontal and cingulate) brain regions modulated by serotonin and dopamine neurotransmission (Kupfer et al., 2012).

A majority of reported functional magnetic resonance imaging (fMRI) studies in MDD has applied stimulus-based acquisition protocols. Participants were confronted with predefined stimuli in the scanner, e.g. pictures of emotional faces. Brain activity in response to these stimuli was analyzed (Groenewold et al., 2013; Fitzgerald et al., 2008; Diener et al., 2012; Delvecchio et al., 2012; Stuhrmann et al., 2011). Stimulus-based fMRI requires rather complex experimental setups. In contrast, fMRI at rest, so-called resting-state fMRI (rs-fMRI), facilitates the examination of spontaneous neural activity in networks that highly resemble those observed in task-based fMRI (Smith et al., 2009). It necessitates simpler, but nonetheless highly standardized procedures (Van Dijk et al., 2010) and has therefore attracted attention by researchers interested in clinical applications of fMRI (Lee et al., 2012; Zhang and Raichle, 2010; Sundermann et al., 2014).

Analyses of rs-fMRI data are usually either based on regional features or on connectivity of distant brain regions. Typical regional measures include regional homogeneity (ReHo) or the (fractional) amplitude of characteristic low-frequency fluctuations (ALFF or fALFF). Functional connectivity (FC) can be operationalized as the temporal correlation of signal fluctuations in remote brain areas. Conventional FC-analyses are seed-based but FC-analyses in a wider sense include independent component analyses or complex graph theoretical network measures. A minority of studies has applied analyses of effective connectivity (such as Granger causality taking temporal dependencies into account) (Margulies et al., 2010; van den Heuvel and Hulshoff Pol, 2010). Rs-fMRI is increasingly adopted scientifically in subjects with MDD (Wang et al., 2012; Kühn and Gallinat, 2013). Despite the qualitative similarity of networks observed during task-fMRI and rs-fMRI it has not been firmly established which features of stimulus-related neural correlates of MDD can be sufficiently captured by rs-fMRI. The exact relation of rs-fMRI and other neuroimaging methods at rest including positron emission tomography (PET) is still subject to ongoing research as well (Chetelat et al., 2013; Riedl et al., 2014).

Whereas most neuroimaging studies in MDD focus on disease mechanisms at the group level, there is substantial interest in identifying biomarkers that are clinically applicable

as diagnostic tools in single subjects (Mossner et al., 2007; Atluri et al., 2013; Schneider and Prvulovic, 2013). Particularly, important recent approaches for diagnostic classification in various mental disorders are based on the combination of rs-fMRI with multivariate pattern analysis techniques (MVPA) (Orru et al., 2012; Zarogianni et al., 2013; Klöppel et al., 2011; Sundermann et al., 2014). Seminal work in this field has been done in subjects with MDD (Craddock et al., 2009). Functional neuroimaging data are typically rather noisy and high-dimensional. Therefore, different feature selection (FS) methods have been proposed to identify a subset of most informative features to be used with the aim to increase classification accuracy (Pereira et al., 2009). There is a fundamental distinction between FS approaches using prior knowledge (Chu et al., 2012) and data-driven methods, particularly filters or wrappers, that use the training dataset itself for FS (Pereira et al., 2009; Mwangi et al., 2013). Recent evidence from structural neuroimaging in dementia indicates that FS based on prior knowledge may be advantageous. In that report support vector machines (SVM) were used for classification (Chu et al., 2012). Such kernel methods like SVM are especially popular in recent attempts to classify fMRI datasets (Orru et al., 2012; Sundermann et al., 2014).

There seems to be a substantive body of scientific studies on rs-fMRI in MDD now. However methods of data analysis and results are very heterogeneous. Previous efforts to summarize these findings have focused on specificity and interpretability regarding disease mechanisms and therefore adopted rather exclusive study selection criteria (Kühn and Gallinat, 2013) or qualitative methods of data synthesis (Wang et al., 2012). Consequently, they are not optimally suited to select brain areas that contain particularly important information for clinical decisions in MDD.

Purpose of this meta-analysis is to consolidate spatial information about alterations of spontaneous brain activity in patients with unipolar depression compared to healthy controls. This investigation is primarily intended to generate and make available “prior knowledge” that can be readily used as spatial hypotheses in rs-fMRI studies in MDD. This includes but is not limited to pre-selection of features for diagnostic MVPA approaches. In addition results are compared with well-established resting-state networks (RSNs) and spatial representations of recently introduced temporally independent functional modes (TFMs) in the human brain to generate network-based hypotheses to be tested in further investigations. By emphasizing spatial precision and sensitivity this approach only provides limited information about the exact functional nature of altered spontaneous brain activity in MDD.

2. Materials and Methods

2.1 Identification and selection of relevant studies

We conducted a PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) search using the following query on August 20, 2013: *("depression" OR "depressive") AND ("fMRI" OR "functional MRI" OR "functional magnetic") AND ("functional connectivity" OR "resting state" OR "resting-state").*

Initially, 183 results were identified. In addition, we also screened a recent review for further papers (Wang et al., 2012) and a prior rather exclusive meta-analysis (Kühn and Gallinat, 2013) comprising rs-fMRI alterations in depression. Thereby six additional articles were identified. Titles and abstracts were manually screened twice (by two individuals, BS and MOLB) for studies (in English language) reporting results on rs-fMRI in adult patients with typical subtypes of unipolar depression (not adolescent, postpartum and late-life depression as well as studies that aimed at investigating a specific comorbidity) compared to healthy controls. Of these 51 studies identified, whole text versions were screened for studies fulfilling these criteria as well as including at least 10 subjects per group and reporting resulting coordinates of group comparisons (depression versus healthy controls) in either MNI/ICBM (Mazziotta et al., 2001) or Talairach (Talairach, 1988) space. 32 studies fulfilled these criteria and were therefore included in the final analyses. Studies by the same authors were screened for highly similar demographical characterization of samples and were otherwise considered independent in further analyses based on consensus of BS, BP and MOLB.

2.2 Coordinate-based meta-analysis

Reported maxima coordinates were extracted and, if reported in Talairach space, converted to MNI space using tal2icbm (Lancaster et al., 2007; Laird et al., 2010). As an exception, coordinates from one study (Lui et al., 2011) were transformed using tal2mni (Brett et al., 2001) as final coordinates in that study had initially been transformed using this method. Coordinates were assigned to two categories based on directionality of findings in order to avoid that clearly opposed findings in the original studies enhance each other in the ALE-analysis: Group A comprises findings of decreased long distance or local connectivity (including lower correlation coefficients or lower regional homogeneity) or lower power of typical low frequency fluctuations representing spontaneous neural activity in depression compared to healthy controls and findings without clearly interpretable directionality information (Wang et al., 2013; Wang et al., 2012; Wang et al., 2013; Guo et al., 2013; Guo et al., 2012; Liu et al., 2013; Guo et al., 2013; Guo et al., 2013; Ma et al., 2013; Zeng et al., 2013; Liu et al., 2013; Tang et al., 2013; Peng

et al., 2012; Peng et al., 2011; Guo et al., 2012; Ma et al., 2012; Ye et al., 2012; Zhu et al., 2012; Guo et al., 2011; Guo et al., 2011; Furman et al., 2011; Veer et al., 2010; Wu et al., 2011; Liu et al., 2010; Hamilton et al., 2011; Zhou et al., 2010; Yao et al., 2009; Bluhm et al., 2009; Lui et al., 2011; Greicius et al., 2007). Details of these studies are presented in table 1. Group B represents increased connectivity or low frequency fluctuations in depression compared to controls (table 2) (Wang et al., 2013; Wang et al., 2012; Guo et al., 2013; Guo et al., 2013; Liu et al., 2013; Liu et al., 2013; Guo et al., 2012; Ma et al., 2012; Ye et al., 2012; Zhu et al., 2012; Cao et al., 2012; Guo et al., 2011; Guo et al., 2011; Furman et al., 2011; Veer et al., 2010; Wu et al., 2011; Liu et al., 2010; Sheline et al., 2010; Hamilton et al., 2011; Zhou et al., 2010).

Table 1 - Studies in group A (representing mainly decreased connectivity / function in depression and ambiguous directionality). Individual reports are grouped by samples according to potential overlap.

Sample number	Author and year	Samle size and depression subtype	Medication	primary analysis method
1	(Wang et al., 2013)	14 (MDD, first episode), 14 (HC)	partially	ReHo
	(Wang et al., 2013)	17 (MDD, first episode), 17 (HC)	no	VMHC
	(Wang et al., 2012)	18 (MDD, first episode), 18 (HC)	no	(f)ALFF
2	(Guo et al., 2013)	22 (MDD, treatment resistant), 23 (MDD, treatment sensitive), 19 (HC)	yes	VMHC
	(Guo et al., 2012)	22 (MDD, treatment resistant), 23 (MDD, treatment sensitive), 19 (HC)	yes	ReHo-based
	(Liu et al., 2013)	22 (MDD, first episode), 19 (HC)	no	fALFF
3	(Guo et al., 2013)	24 (MDD, first episode), 24 (HC)	no	fALFF, Seed-FC (Cerebellum)
	(Guo et al., 2013)	24 (MDD; first episode), 24 (HC)	no	VMHC
4	(Zeng et al., 2013)	24 (MDD), 29 (HC)	no	seed-FC (anterior cingulate)
	(Ma et al., 2013)	24 (MDD), 29 (HC)	no	seed-FC (cerebellum)
5	(Liu et al., 2013)	22 (MDD), 26 (HC)	yes	fALFF
6	(Tang et al., 2013)	28 (MDD), 30 (HC)	no	seed-FC (amygdala)
7	(Peng et al., 2012)	16 (MDD), 16 (HC)	no	seed-FC (anterior cingulate)
	(Peng et al., 2011)	16 (MDD), 16 (HC)	no	ReHo
8	(Ma et al., 2012)	18 (MDD, treatment resistant), 17 (MDD, treatment sensitive) 17 (HC)	yes	seed-FC (based on gray matter abnormalities)
	(Guo et al., 2012)	18 (MDD, treatment resistant), 17 (MDD, treatment sensitive)	yes	ALFF

		17 (HC)		
9	(Ye et al., 2012)	22 (MDD, first episode), 30 (HC)	no	seed-FC (right DLPFC)
10	(Zhu et al., 2012)	35 (MDD, first episode), 35 (HC)	no	ICA
11	(Guo et al., 2011)	17 (MDD), 17 (HC)	yes	ReHo
	(Guo et al., 2011)	24 (MDD, treatment resistant) 19 (MDD, treatment resistant)	yes	ReHo
12	(Furman et al., 2011)	21 (MDD, women only), 19 (HC, women only)	yes	seed-FC (striatum)
13	(Veer et al., 2010)	19 (MDD), 19 (HC)	no	ICA
14	(Wu et al., 2011)	22 (MDD, treatment resistant), 26 (HC)	yes	ReHo
15	(Liu et al., 2010)	14 (MDD), 15 (HC)	no	ReHo
16	(Hamilton et al., 2011)	16 (MDD), 14 (HC)	no	Granger causality
17	(Bluhm et al., 2009)	14 (MDD), 15 (HC)	no	seed-FC (precuneus / posterior cingulate cortex)
18	(Yao et al., 2009)	22 (MDD), 22 (HC)	partially	ReHo
19	(Greicius et al., 2007)	28 (MDD), 20 (HC)	yes	ICA
20	(Lui et al., 2011)	32 (MDD, treatment sensitive), 28 (MDD, treatment resistant), 48 (HC)	yes	seed-FC (multiple)
21	(Zhou et al., 2010)	18 (MDD), 20 (HC)	no	seed-FC (multiple)

HC: healthy controls, MDD: major depressive disorder, FC: functional connectivity, ReHo: regional homogeneity, (f)ALFF: (fractional) amplitude of low frequency fluctuations, VMHC: voxel-mirrored homotopic connectivity, ICA: independent component analysis, DLPFC: dorsolateral prefrontal cortex

Table 2 – Studies in group B (representing mainly increased connectivity / function in depression). Individual reports are grouped by samples according to potential overlap.

Sample number	Author and year	Sample size and depression subtype	Medication	primary analysis method
1	(Wang et al., 2013)	14 (MDD, first episode), 14 (HC)	partially	ReHo
	(Wang et al., 2012)	18 (MDD, first episode), 18 (HC)	no	(f)ALFF
2	(Guo et al., 2013)	24 (MDD, first episode), 24 (HC)	no	fALFF, Seed-FC (Cerebellum)
	(Guo et al., 2013)	24 (MDD, first episode), 24 (HC)	no	VMHC
3	(Liu et al., 2013)	22 (MDD), 26 (HC)	yes	fALFF
4	(Liu et al., 2013)	22 (MDD, first episode), 19 (HC)	no	fALFF
5	(Peng et al., 2012)	16 (MDD), 16 (HC)	no	seed-FC (anterior cingulate)
6	(Ma et al., 2012)	18 (MDD, treatment resistant), 17 (MDD, treatment sensitive) 17 (HC)	yes	seed-FC (based on gray matter abnormalities)

	(Guo et al., 2012)	18 (MDD, treatment resistant), 17 (MDD, treatment sensitive) 17 (HC)	yes	ALFF
7	(Ye et al., 2012)	22 (MDD, first episode), 30 (HC)	no	seed-FC (right DLPFC)
8	(Cao et al., 2012)	42 (MDD), 32 (HC)	no	seed-FC (hippocampus)
9	(Zhu et al., 2012)	35 (MDD, first episode), 35 (HC)	no	ICA
10	(Guo et al., 2011)	17 (MDD), 17 (HC)	yes	ReHo
	(Guo et al., 2011)	24 (MDD, treatment resistant) 19 (MDD, treatment resistant)	yes	ReHo
11	(Furman et al., 2011)	21 (MDD, women only), 19 (HC, women only)	yes	seed-FC (striatum)
12	(Veer et al., 2010)	19 (MDD), 19 (HC)	no	ICA
13	(Wu et al., 2011)	22 (MDD, treatment resistant), 26 (HC)	yes	ReHo
14	(Sheline et al., 2010)	18 (MDD), 17 (HC)	no	seed-FC (multiple)
15	(Liu et al., 2010)	14 (MDD), 15 (HC)	no	ReHo
16	(Hamilton et al., 2011)	16 (MDD), 14 (HC)	no	Granger causality
17	(Zhou et al., 2010)	18 (MDD), 20 (HC)	no	seed-FC (multiple)

HC: healthy controls, MDD: major depressive disorder, FC: functional connectivity, ReHo: regional homogeneity, (f)ALFF: (fractional) amplitude of low frequency fluctuations, VMHC: voxel-mirrored homotopic connectivity, ICA: independent component analysis, DLPFC: dorsolateral prefrontal cortex

Coordinate-based meta-analyses were calculated with GingerALE (Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX, USA, version 2.3.1, http://www.brainmap.org/ale/) using the non-additive activation likelihood estimation (ALE) approach with coordinates organized by subject group (ALE-S method) to account for non-independent samples (Turkeltaub et al., 2012). ALE-S is an extension of the random effects ALE approach (Eickhoff et al., 2009) that prevents multiple experiments performed by one subject group from cumulatively influencing ALE values. Therefore a modelled activation map is generated for each subject group independently based on published coordinates in a first step. These maps are then combined in a second step to calculate final ALE values (Turkeltaub et al., 2012). Coordinates in group A were assigned to 21, in group B to 17 presumably independent subjects groups as indicated in tables I and II. After excluding 11 locations in group A and 7 locations in group B which are potentially located outside the gray matter by masking coordinates using the conservative standard mask in GingerALE 305 (group A) and 132 (group B) foci remained. Study specific smoothing using a Gaussian kernel (group A: FWHM median = 9.17 mm, range 8.88 to 9.57 mm, group B: FWHM median = 9.28 mm, range 8.87 to 9.50 mm) was applied based on the mean sample size per subject group to take

different sample sizes into account. Results were thresholded at $p < 0.05$ corrected for multiple comparisons using cluster-based correction with a cluster-forming threshold of $p < 0.01$ (uncorrected) and 1000 permutations (Eickhoff et al., 2012) resulting in a minimum cluster size of 528 mm^3 in group A and 544 mm^3 in group B. All analyses were calculated in MNI space.

Anatomical labels were automatically assigned in GingerALE. Visualizations were created using Mango (Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX, USA, version 3.0.4, http://ric.uthscsa.edu/mango/) and a high resolution anatomical template with isotropic voxels in MNI space as distributed with GingerALE.

2.3 Assessment of conjunction with functional networks

Maps of meta-analytic results in MNI space were overlaid and compared with maps of published RSNs and TFMs (Smith et al., 2012) based on publicly available data from the WU-Minn Human Connectome Project (1U54MH091657), funded by the 16 NIH Institutes and Centers that Support the NIH Blueprint for Neuroscience Research. Correspondence of RSNs or TFMs with meta-analytic results was judged by consensus of BS and BP. In contrast to RSNs, TFMs emphasize the temporal instead of the spatial independence of functionally connected brain areas and thus represent an alternative approach to defining functional networks. While RSN- and TFM-subcomponents resemble each other, the overall combination of these regions can be quite different, potentially depicting an at least equally valid aspect of functional brain organization (Smith et al., 2012).

3. Results

3.1 Decreased or ambiguously altered FC in MDD

Results of group A spatially converged mainly in the left superior/middle temporal gyrus and bilaterally in the insula, precuneus, superior frontal gyrus, lentiform nucleus and thalamus. For detailed results see figure 1A, figure 1C and table 3. Complete thresholded ALE-maps are made available in NIfTI-1 data format as supplementary material.

Table 3 – Brain areas (cluster-information and peak voxels) with significant convergence across studies in Group A (mainly decreased connectivity / activity in depression)

		(Sub-)Maxima coordinates			
Anatomical label	BA	x	y	z	ALE
Cluster 1 (4 contributing subject groups, volume: 1048 mm3, weighted center: x = -59, y = -9, z = 2)					
Left Superior Temporal Gyrs	22	-60	-10	2	0.017
Cluster 2 (4 contributing subject groups, volume: 960 mm3, weighted center: x = -36, y = 7, z = -14)					
Left Superior Temporal Gyrus	38	-36	2	-18	0.016
Left Insula	13	-36	12	-10	0.014
Cluster 3 (3 contributing subject groups, volume: 960 mm3, weighted center: x = 42, y = -1, z = 2)					
Right Claustrum		40	-2	2	0.019
Right Insula	13	48	4	2	0.010
Cluster 4 (3 contributing subject groups, volume: 952 mm3, weighted center: x = -56, y = -32, z = -13)					
Left Middle Temporal Gyrus	21	-58	-30	-16	0.015
Left Middel Temporal Gyrus	20	-54	-36	-10	0.013
Cluster 5 (3 contributing subject groups, volume: 856 mm3, weighted center: x = 15, y = -66, z = 26)					
Right Precuneus	31	16	-66	26	0.016
Cluster 6 (3 contributing subject groups, volume: 840 mm3, weighted center: x = 9, y = -51, z = 46)					
Right Precuneus	7	8	-52	46	0.016
Cluster 7 (3 contributing subject groups, volume: 656 mm3, weighted center: x = 27, y = 6, z = -3)					
Right Putamen		30	4	0	0.013
Right Putamen		24	6	-6	0.011
Cluster 8 (2 contributing subject groups, volume: 616 mm3, weighted center: x = 15, y = -25, z = -2)					
Right Thalamus		14	-26	-2	0.016
Cluster 9 (3 contributing subject groups, volume: 608 mm3, weighted center: x = -53, y = -24, z = 7)					
Left Superior Temporal Gyrus	41	-54	-24	6	0.015
Cluster 10 (4 contributing subject groups, volume: 584 mm3, weighted center: x = -4, y = -18, z = 4)					
Left Thalamus (Medial Dorsal Nucleus)		-4	-16	6	0.012
Left Thalamus		-6	-22	-2	0.010
Right Thalamus		4	-20	6	0.009
Cluster 11 (2 contributing subject groups, volume: 528 mm3, weighted center: x = 22, y = 62, z = 12)					
Right Superior Frontal Gyrus	10	22	62	10	0.012
Right Superior Frontal Gyrus	10	22	62	8	0.011

Right Superior Frontal Gyrus	10	30	60	6	0.009

p < 0.05 with cluster-based thresholding to correct for multiple comparisons, coordinates reported in MNI space, anatomical labels representing nearest gray matter locations, contributing subjects groups only denotes groups with original foci located within the resulting cluster

3.2 Increased FC in MDD

Findings in group B mainly comprised the pre-/subgenual anterior cingulate cortex and neighboring medial frontal cortex, the precuneus and neighboring posterior cingulate cortex, lateral prefrontal cortex bilaterally with a left predominance, left lateral parietal cortex as well as the right hippocampus and right cerebellum. Detailed results are presented in figure 1B, figure 1C and table 4. For thresholded ALE-maps see the supplementary material.

Table 4 – Brain areas (cluster-information and peak voxels) with significant convergence across studies in Group B (increased connectivity / activity in depression)

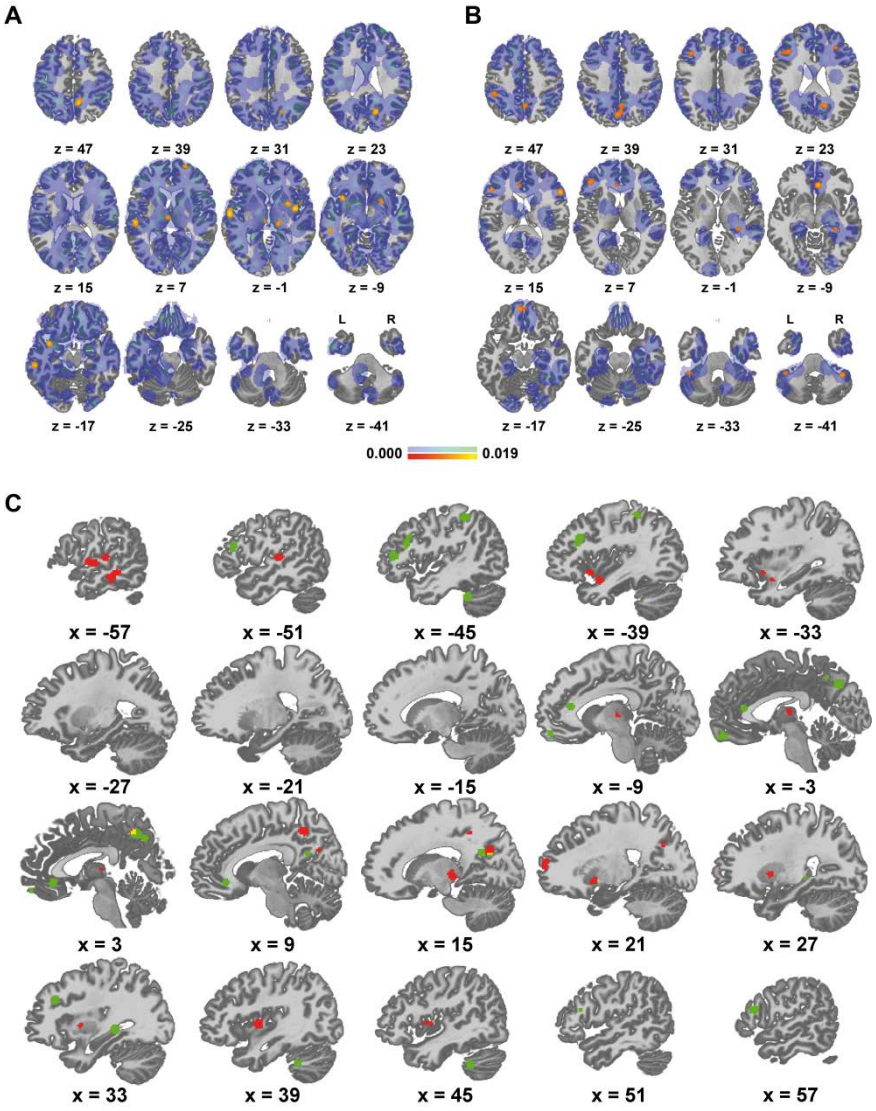
		(Sub-)Maxima coordinates			
Anatomical label	BA	x	y	z	ALE
Cluster 1 (3 contributing subject groups, volume: 1792 mm3, weighted center: x = 1, y = -63, z = 41)					
Left Precuneus	7	2	-56	44	0.015
Left Cuneus	7	-2	-70	38	0.014
Cluster 2 (4 contributing subject groups, volume: 1704 mm3, weighted center: x = -43, y = 25, z = 24)					
Left Middle Frontal Gyrus	46	-48	26	18	0.012
Left Middle Frontal Gyrus	9	-38	24	28	0.011
Left Middle Frontal Gyrus	9	-40	26	22	0.010
Cluster 3 (3 contributing subject groups, volume: 928 mm3, weighted center: x = -42, y = -39, z = 52)					
Left Inferior Parietal Lobule	40	-42	-40	52	0.013
Cluster 4 (2 contributing subject groups, volume: 896 mm3, weighted center: x = -3, y = 56, z = -18)					
Left Medial Frontal Gyrus	10	-6	56	-16	0.012
Left Medial Frontal Gyrus	10	0	60	-20	0.009
Right Medial Frontal Gyrus	10	2	56	-18	0.008
Cluster 5 (2 contributing subject groups, volume: 736 mm3, weighted center: x = 6, y = 33, z = -10)					
Right Anterior Cingulate Cortex	24	6	34	-10	0.015
Cluster 6 (2 contributing subject groups, volume: 688 mm3, weighted center: x = -44, y = -42, z = -36)					
Left Cerebellum (Anterior Lobe, Culmen)		-44	-42	-36	0.015
Cluster 7 (2 contributing subject groups, volume: 680 mm3, weighted center: x = 33, y = -34, z = -4)					
Right Hippocampus		32	-34	-4	0.015

Cluster 8 (2 contributing subject groups, volume: 680 mm3, weighted center: x = 15, y = -58, z = 23)					
Right Posterior Cingulate Cortex	31	16	-56	24	0.011
Right Precuneus	31	14	-66	22	0.008
Cluster 9 (2 contributing subject groups, volume: 664 mm3, weighted center: x = -43, y = 39, z = 8)					
Left Middle Frontal Gyrus	46	-44	38	8	0.011
Cluster 10 (2 contributing subject groups, volume: 648 mm3, weighted center: x = 57, y = 22, z = 17)					
Right Inferior Frontal Gyrus	9	56	22	18	0.015
Cluster 11 (2 contributing subject groups, volume: 624 mm3, weighted center: x = 43, y = -45, z = -42)					
Right Cerebellum (Tonsil)		44	-44	-42	0.012
Cluster 12 (2 contributing subject groups, volume: 624 mm3, weighted center: x = -5, y = 34, z = 12)					
Left Anterior Cingulate Cortex	24	-6	34	12	0.013
Cluster 13 (2 contributing subject groups, volume: 592 mm3, weighted center: x = 34, y = 31, z = 28)					
Right Middle Frontal Gyrus	9	34	30	28	0.013

$p < 0.05$ with cluster-based thresholding to correct for multiple comparisons, coordinates reported in MNI space, anatomical labels representing nearest gray matter locations, contributing subjects groups only denotes groups with original foci located within the resulting cluster

3.3 Correspondence with functional networks

Single local maxima of these results corresponded with single RSN subregions, mainly posterior aspects of the DMN and lateral frontal areas with fronto-parietal RSNs. However, there was no RSN that spanned larger aspects of the meta-analytic results. In contrast one TFM, TFM 21 in the original publication (Smith et al., 2012), exhibited a good correspondence with a larger set of meta-analytically derived clusters from group B (Figure 2). This TFM comprises DMN areas anticorrelated with lateral-frontal regions often seen as part of an executive control or cognitive control network (Smith et al., 2012). Left lateral frontal areas and the posterior cingulate / precuneus cluster in group B representing increased connectedness in MDD correspond with positive connectivity in this TFM. In addition, the left parietal cluster in group B corresponds to a negatively correlated area included in the data on this TFM.



191 **Figure 1** – Areas of altered functional connectivity / activity in depression compared
192 to controls: (A) red to yellow: significant meta-analytic results ($p < 0.05$) in group A
193 (representing mainly decreased connectivity / function in depression), blue to green:
194 unthresholded ALE values, (B) equivalent representation of group B (increased
195 connectivity / function in depression), (C) qualitative display of significant results, red:
196 group A, green: group B, yellow: overlap

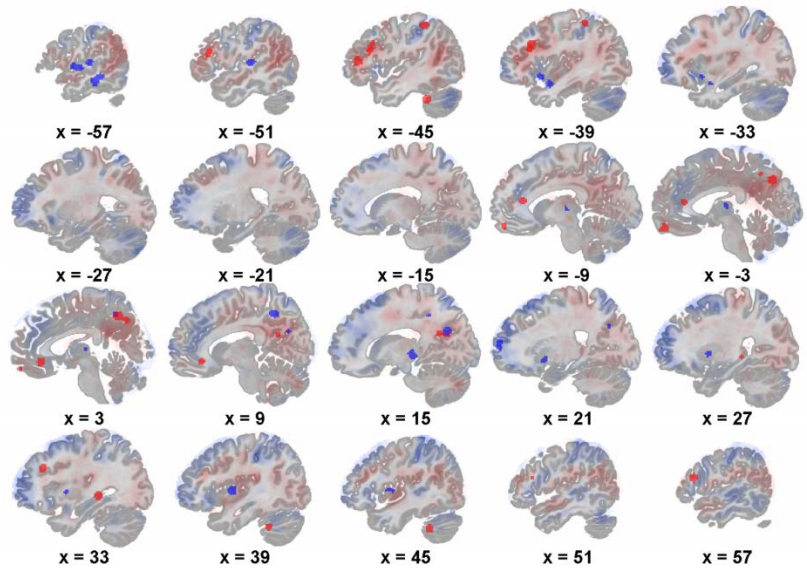


Figure 2 – Areas of altered functional connectivity / activity in depression ($p < 0.05$) compared to controls overlayed with TFM 21 (semi-transparent) from (Smith et al., 2012); blue: group A, red: group B

4. Discussion

4.1 Correspondence with functional networks

In terms of classical RSNs several clusters of altered FC in MDD correspond either to midline structures as DMN subregions (Fox et al., 2005; Smith et al., 2012) or lateral frontal areas within a fronto-parietal network (Smith et al., 2012) associated with cognitive control (Niendam et al., 2012). However, neither one of these network definitions comprehends the major meta-analytical findings nor do these point towards all major subregions of these networks. Results therefore seem to represent interactions between these major classical RSNs.

Such interactions have recently been addressed using a different operationalization of network identification in rs-fMRI data, so-called TFMs (Smith et al., 2012). Indeed, the spatial representation of one of these TFMs seems to better comprehend rs-fMRI alterations in MDD observed here. Analyses focusing on temporal dynamics of spontaneous brain activity assuming non-stationarity of functional networks, such as TFMs, seem to be at least as valid and biologically plausible as those aiming at classical RSNs. Still, the exact neurophysiological nature of TFMs has to be elucidated by further research (Hutchison et al., 2013). Due to the nature of the studies underlying this meta-analysis the exact temporal characteristics can, however, not be explored here. Thus the

observation of a good correspondence with this TFM is only an exploratory result and should be tested in further studies. The original definition of this TFM 21 relied upon fMRI data acquisition techniques with increased temporal resolution (Ugurbil et al., 2013; Smith et al., 2013). Thus it seems desirable as well to investigate if such faster data sampling can improve diagnostic classification in MDD.

As a notable finding, the subgenual ACC peak coordinates observed were not well captured by either RSNs or TFMs. Generally, results of group B seem to better correspond to RSNs or TFMs as more heterogeneously appearing results of group A.

4.2 Comparison of results with additional functional neuroimaging results in MDD and functional implications

First a subset of studies that did not fulfill the inclusion criteria, mostly because of missing coordinate data, but relate to the main meta-analytic findings are discussed. In a study using independent component analyses (ICA) (Li et al., 2013) a distinction of the DMN into an anterior and a posterior component was addressed. Both showed increased FC before treatment. Differences in the posterior DMN were normalized after antidepressant treatment, while abnormal FC persisted within the anterior DMN (Li et al., 2013). This distinction potentially relates to the fact that only one of these components was significantly identified across studies. Zhang et al. adopted graph theoretical measures to study the topological organization on networks in MDD. Patients exhibited increased nodal centralities, predominately in the caudate nucleus and DMN as well as reduced nodal centralities in occipital, orbitofrontal and temporal regions (Zhang et al., 2011). In another recent rs-fMRI study, published after the date of study identification for this analysis, Sambataro et al. also highlight a differential involvement of DMN subsystems in MDD: Patients exhibited increased connectivity of ventral, posterior and core DMN components. The interplay from the anterior to the ventral DMN subsystems was reduced (Sambataro et al., 2013). These findings are in line with meta-analytically observed increases in spontaneous activity in some but not all DMN subregions.

Brain activity at rest has also been studied using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). In contrast to rs-fMRI analyses these studies rarely adopt FC measures. In an ALE meta-analysis Fitzgerald et al. report a complex pattern of predominantly frontal alterations of brain activity featuring medial frontal hypoactivity, heterogenous findings regarding directionality of alterations in lateral frontal areas in both cerebral hemispheres and hyperactivity in the thalami (Fitzgerald et al., 2008). There is a fair spatial overlap with rs-fMRI findings but the

directionality of alterations is not directly comparable. However, in an exclusive analysis of only four studies using 18F-Fluorodeoxyglucose-PET, regionally increased glucose metabolism was observed near the subgenual ACC (Sacher et al., 2012), an area of increased activity / connectivity observed by rs-fMRI. As a notable aspect, early results of single PET studies of increased brain activity in MDD in the subgenual ACC, orbitofrontal cortex, ventrolateral prefrontal cortex, thalamus as well as the amygdala and less-markedly even medial parietal areas who have substantially informed current integrated neurocircuitry models of mood disorders (Price and Drevets, 2010) exhibit a better correspondence with rs-fMRI results than the meta-analytic reports of PET-studies in MDD. Thus it seems desirable to investigate in further studies if features selected by rs-fMRT itself are better suited than PET-derived features that have been used in previous MVPA studies in MDD, for example (Craddock et al., 2009). However, this issue cannot be finally resolved at the moment as there is no consensus regarding optimal classification algorithms for diagnostic purposes (Sundermann et al., 2014).

In a comprehensive voxel-based meta-analysis of 22 task-based functional neuroimaging studies (fMRI, ^{15}O-H_2O PET, ^{99m}Tc-ethyl-cysteinate-dimer SPECT) on altered emotion and cognition in MDD a rather heterogenous set of brain regions with altered activity spanning all lobes of the telencephalon as well as the thalamus and striatum was observed. Some of these regions exhibited consistent hyper- other hypo-activity in response to cognitive or emotional challenge but there were also areas with coincidental hyper- and hypoactivity (Diener et al., 2012). Those results in task-fMRI correspond only moderately with findings in rs-fMRI reported here: There was a lateral frontal (Brodmann area 9) increase in task-related activity in MDD compared to controls as well as increased spontaneous activity / connectivity at rest. Insular, thalamic and striatal activity exhibited comparable directionality of findings as well. However, task-based fMRI did not reveal consistent alterations of activity in posterior DMN components or the subgenual ACC. Thus rs-fMRI may be better suited to depict these systems presumably involved in MDD pathophysiology. However, the heterogeneity of findings may also be attributable to the heterogeneity of analysis methods and true biological as well as treatment-associated variability in the original samples.

In another voxel-based meta-analysis on methodologically more homogenous fMRI studies of facial affect processing, a widely used paradigm in MDD research, only increased engagement of few limbic regions (amygdala and parahippocampal gyrus) and a relative hypoactivation of the striatum were observed (Delvecchio et al., 2012). Thus there was only fair correspondence with rs-fMRI results. However, results reported in another voxel-based meta-analysis (Fitzgerald et al., 2008) and a more comprehensive

systematic review (Stuhrmann et al., 2011) of facial emotion processing exhibited a slightly better spatial correspondence with rs-fMRI results. As a notable finding, alterations of amygdala activity or connectivity were not consistently observed in rs-fMRI. It has been highlighted, that even the directionality of amygdala activity is highly dependent on the emotional valence of stimuli (Groenewold et al., 2013). Therefore, this dynamical aspect of potential disease mechanisms in MDD may not be sufficiently captured by potential diagnostic classification efforts based on spontaneous activity only. But relying on amygdala activity diagnostically may complicate the differentiation of patients with anxious comorbidity, which is an important symptom in a subset of patients with MDD (Kupfer et al., 2012).

The abnormal interplay of cortical midline structures associated with self-referential processing, emotion-related brain areas and lateral cortical areas related to higher cognitive processing has been functionally interpreted as a correlate of pathologically increased ruminative brooding in MDD. In particular, a reduced top-down inhibition of cortical midline and limbic regions has been discussed (Nejad et al., 2013; Marchetti et al., 2012).

4.3 Comparison of results with structural neuroimaging in depression

There are repeated and meta-analytically ascertained reports about specific regional volume reductions in MDD affecting the basal ganglia, hippocampus, frontal lobe (including the orbitofrontal cortex) and less consistently the cingulate cortex and thalamus (Arnone et al., 2012; Koolschijn et al., 2009; Kempton et al., 2011; Lorenzetti et al., 2009). Though these reported locations, based on anatomical descriptors, resemble a subset of findings in rs-fMRI, a strict formal comparison is not feasible as results were mostly not reported in a common coordinate space. Another voxel-based meta-analysis of volumetric studies (Sacher et al., 2012) reports only weak convergences of findings across studies. However that analysis might have been underpowered with only six studies fulfilling the inclusion criteria. Posterior midline structures, central locations of aberrant spontaneous brain activity in MDD, do not seem to be significantly affected by these volume reductions.

Moreover, morphological imaging in MDD revealed moderate increases in white matter hyperintensities based on T2-weighted imaging as a common finding at the group level (Kempton et al., 2011; Arnone et al., 2012). Though white matter hyperintensities are a common finding, they can reflect small vessel disease and are therefore associated with an increased risk of cardiovascular events, dementia and death within a studied period (Debette and Markus, 2010).

White matter microstructure as an important aspect of suspected network pathology in affective disorders has been studied using diffusion tensor imaging (DTI) and derivative techniques: As a meta-analytically ascertained finding, reduced anisotropy, a potential measure of fiber integrity, was observed in parts of the superior frontal white matter presumed to connect the dorsolateral prefrontal cortex and anterior cingulate cortex with subcortical nuclei (Sexton et al., 2009). Another meta-analysis, specifically focusing on voxel-based analyses of fractional anisotropy (FA) in depression reported decreased FA in the superior longitudinal fasciculus and increased FA in the fronto-occipital fasciculus in MDD (Murphy and Frodl, 2011). The subgenual ACC associated with increased spontaneous activity / connectivity was identified as a potential site for therapeutic deep brain stimulation in MDD (Johansen-Berg et al., 2008; Coenen et al., 2011; Mayberg et al., 2005; Lozano et al., 2008). The structural connectivity of this area has been investigated using diffusion imaging demonstrating widely distributed connectivity with frontal, limbic and visceromotor brain regions. An associated connectivity-based parcellation of the perigenual ACC revealed two distinct subdivisions with distinct connectivity profiles, the pre- and the subgenual ACC. While both subregions are connected with the midcingulate cortex, frontal pole, hypothalamus and nucleus accumbens, the subgenual ACC was connected more strongly with the orbitofrontal cortex, medial temporal lobe and through the fornix (Johansen-Berg et al., 2008). The subgenual ACC observed in this meta-analysis of rs-fMRI data corresponds well with the latter location defined by distinct structural connectivity features.

Results of functional and structural imaging in MDD seem somewhat contradictory: Some areas with increased spontaneous activity / functional connectivity seem to exhibit volume reduction or are served by white matter tracts with decreased anisotropy. Though functional and structural connectivity metrics show mostly concordant variations (Honey et al., 2010; Damoiseaux and Greicius, 2009), there are other examples of a similar paradox, e.g. in multiple sclerosis (Hawellek et al., 2011).

4.4 Potential applications

Results presented here can be used as prior knowledge about spatial locations of altered spontaneous brain activity in MDD. This includes definition of regions of interest for hypothesis-driven group comparisons and particularly for FS (Mwangi et al., 2013; Pereira et al., 2009; Chu et al., 2012) in diagnostic classification efforts based on rs-fMRI data. For approaches using correlation based on seeds or pairs of regions of interest (Margulies et al., 2010), coordinates from tables III and IV can be used. In addition, most software tools for voxel-based classification facilitate masking for FS (Schrouff et al.,

2013). Therefore NIfTI-files of thresholded ALE-maps in MNI space are provided (supplementary material).

A different approach is to use corresponding representations of established functional networks in the brain instead of the original results to enhance biological plausibility of analyses. However, although primarily subregions of the DMN and a cognitive control network seem to be affected, the overall correspondence of results with a single classical RSN is at best moderate. We hypothesize that a recently defined TFM, supplied as a parametric map of TFM 21 in NIfTI-1 data format through the authors of the original study (Smith et al., 2012), may be an appropriate substitute as a mask in voxel-based approaches.

4.5 Limitations of the current analysis

The analysis predominantly provides information about spatial congruency of resting-state fMRI findings in depression. It does, however, not allow estimation of effect sizes. Information about the directionality of supposed alterations of functional connectivity is limited. This especially pertains to the number of different post-processing methodologies used in the studies reviewed. While interpretation of directionality in most of these methods is well-established for the so-called default mode network (Van Dijk et al., 2010) this does not necessarily generalize to other networks.

The ALE-approach adopted here relies on sufficiently reliable studies reporting results in terms of whole brain coordinates. Thus not every study reporting relevant group comparison results based on rs-fMRI data in MDD could be included for this methodological reason. In seed- or ROI-based analyses (Margulies et al., 2010) the original seed coordinates less strictly reflect the spatial location of potentially associated alterations and could therefore not be included in this coordinate-based analysis. This may limit the sensitivity for alterations in such regions that have been regarded of special importance by the authors of the original studies.

The generalizability of results to other samples is also limited by the heterogeneity of samples in the studies included as these range from first-episode medication naïve subjects to treatment resistant patients after multiple depressive episodes. However, the literature currently available does not seem to facilitate a more specific meta-analysis yet. As stated above this meta-analysis primarily pursued a methodological goal and therefore emphasized spatial specificity.

Multiple reports based on the same or similar data and overlapping samples are a generic problem in meta-analyses (Littell et al., 2008). In this work a recent modification

of the ALE method (Turkeltaub et al., 2012) was adopted to minimize within-group effects of potentially overlapping samples without sacrificing valuable information. Despite that, it cannot be fully excluded that there is residual overlap of samples in studies considered independent here. However, we adopted a consensus based approach involving three reviewers to reduce this potential bias.

Even despite this issue the recent literature on rs-fMRI in MDD displays a noticeable tendency towards particular Asian as well as North American or European populations. As prevalence and clinical symptomatology differ significantly between cultural contexts (Yeung and Chang, 2014; Juhasz et al., 2012; Halbreich et al., 2007; Kirmayer, 2001) results reported in this meta-analysis may not necessarily be applicable to other populations.

This meta-analysis focused on comparisons of depressive subjects and healthy controls. However, it seems to be even more desirable to identify differential neuroimaging biomarkers that provide information about individual prognosis or guide therapeutic decisions (Mossner et al., 2007; Sundermann et al., 2014). Feature (pre-)selection for such efforts may be optimized specifically in the future as soon as further rs-fMRI research in these situations becomes available.

5. Conclusion

Resting-state fMRI studies in depression have identified a distributed pattern of brain regions with increased or decreased spontaneous activity compared to healthy controls. The most distinct finding is hyperactivity or hyperconnectivity presumably reflecting the interaction of midline structures (particulary posterior DMN components associated with self-referential processing and the subgenual ACC) with lateral frontal areas related to externally-directed cognition. Alterations that can be captured by rs-fMRI seem to differ from those identifiable with other neuroimaging modalities but show considerable overlap. Results of this meta-analysis can be readily applied for defining ROIs in rs-fMRI studies in MDD including feature selection for diagnostic classification approaches.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

BS and BP conceived and designed the study. MOLB and BS identified and screened the articles. BS, BP and MOLB participated in final study selection and group assignment. BS and MOLB conducted the ALE-analyses. BS and BP compared meta-analytic results with established RSNs and TFMs. BS, BP and MOLB participated in interpretation of the results. BS drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

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