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Review

Is subcortical–cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach

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ABSTRACT

Major depressive disorder has recently been characterized by abnormal resting state hyperactivity in anterior midline regions. The neurochemical mechanisms underlying resting state hyperactivity remain unclear. Since animal studies provide an opportunity to investigate subcortical regions and neurochemical mechanisms in more detail, we used a cross-species translational approach comparing a meta-analysis of human data to animal data on the functional anatomy and neurochemical modulation of resting state activity in depression. Animal and human data converged in showing resting state hyperactivity in various ventral midline regions. These were also characterized by abnormal concentrations of glutamate and γ-aminobutyric acid (GABA) as well as by NMDA receptor up-regulation and AMPA and GABA receptor down-regulation. This cross-species translational investigation suggests that resting state hyperactivity in depression occurs in subcortical and cortical midline regions and is mediated by glutamate and GABA metabolism. This provides insight into the biochemical underpinnings of resting state activity in both depressed and healthy subjects.

Contents

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1. Introduction

Major depressive disorder (MDD) is a psychiatric disorder characterized by depressive symptoms like anhedonia, poor motivation, psychomotor retardation, and ruminations including an increased self-focus (see Thase, 2005; Northoff, 2007). Recent imaging studies demonstrated consistently elevated resting state activity in various cortical and subcortical midline regions like the sub- and perigenual anterior cingulate cortex (PACC), medial prefrontal cortex (PFC), the ventral striatum (VS), and the thalamus (Th) (see reviews and meta-analyses in Fitzgerald et al., 2006, 2007; Greicius et al., 2007; Grimm et al., 2009a,b; Mayberg, 2002, 2003; Phillips et al., 2003). Unfortunately, the exact role of subcortical regions remains unclear due to the limited resolution in human imaging. Moreover, the exact neurochemical mechanisms mediating abnormal resting state activity also remain unclear.

Animal models of depression provide an excellent opportunity to investigate subcortical regions related to primary process emotions and their neurochemical mechanisms in greater anatomical detail compared to human imaging studies (Panksepp, 1998, 2005). Recent animal studies focus on various subcortical regions like the ventral tegmental area (VTA), locus coeruleus (LC), periaqueductal grey (PAG), hypothalamus (Hyp), habenula (Hab), various nuclei of the amygdala (Amyg), bed nucleus of stria terminalis (BNST), dorsal raphe nuclei (DR), nucleus of the solitary tract (NST), basal ganglia, especially the nucleus accumbens (NACC) and caudate-putamen (CP), septum, and thalamic nuclei like the pulvinar and the mediodorsal thalamus (MDT) (see Krishnan and Nestler, 2008; Ressler and Mayberg, 2007; Shumake and Gonzalez-Lima, 2003 for recent reviews). Interestingly, many of these regions show abnormal resting state activity in animal models of depression which may be convergent with human imaging findings. Though one must be cautious when comparing structural and functional neuroanatomy across species, nonetheless there is evidence for many subcortical and cortical homologies across mammals (Cenci et al., 2002; Dalley et al., 2004; Robbins, 1998). A potential relationship of abnormal resting state activity between humans and animals, however, remains to be demonstrated in systematic translational analyses.

Moreover, animal models provide some evidence of GABA and glutamate abnormalities in the very same brain regions showing resting state hyperactivity (see below for details). This raises the question of whether resting state hyperactivity in depression may be due to glutamatergic and GABAergic abnormalities. Though recent animal models have clarified genetic contributions to depression (Cryan and Slattery, 2007; Krishnan and Nestler, 2008; McArthur and Borsini, 2006), neurochemical data in animals may need to be complemented by human data in order to bridge the gap to human clinical issues. This makes it necessary to translate the animal resting state and neurochemical findings into the context of human imaging findings. More specifically, there is a need to merge the observations of abnormal resting state activity in both animals and humans into a common neurochemical model (see Stone et al., 2008; Krishnan and Nestler, 2008 for reviews).

The general aim of this investigation was to develop a cross-species translational pathophysiological model of abnormal resting state activity in MDD. More specifically, our first aim was to directly compare human and animal data on resting state activity in order to yield a common subcortical–cortical network. With this common anatomical model in place, we then aimed to characterize this abnormal subcortical–cortical resting state network in neurochemical terms drawing again on both animal and human data. We hypothesized that increased resting state activity in a ventral anterior subcortical–cortical network, including many limbic regions, may be related to abnormal activity in both glutamatergic and GABAergic metabolism.

To pursue this hypothesis, we performed a two-step investigation. In the first step, we used a systematic meta-analysis of human positron emission tomography (PET) imaging studies in the resting state. The regions identified were then compared with those observed to be abnormal in resting state data of human fMRI studies and animal models; the overall aim was to identify anatomical similarities in the direction of resting state activity showing either hypo- or hyper-activity. The second step consisted of searching for neurochemical abnormalities in those subcortical–cortical regions. Since glutamatergic and GABAergic substances can be investigated in both animals and humans, and have recently been shown to be therapeutically effective in human MDD (see Northoff et al., 1997; Zarate et al., 2006), we then focused on those neurotransmitters. This analysis sheds light on one important aspect of the pathophysiology of depression (i.e. resting state hyperactivity), and thereby may increase our understanding of the biochemical modulation of resting state activity in the default-mode network (Buckner et al., 2008; Raichle et al., 2001; Vincent et al., 2007) in both humans and animals.

2. Materials and methods

2.1. Regional changes and neurochemical modulation of resting state activity in humans

2.1.1. Literature search

To form a dataset of coordinates, we conducted multiple PubMed (http://www.pubmed.gov) searches to initially identify all imaging studies – positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – including patients with depressive disorders published from May 1998 to February 2008. The search included the keywords "depression", "MDD", "PET", "positron emission tomography", "fMRI", and "functional magnetic resonance imaging". In addition, we used the brainmap.org data-base of coordinates by utilizing a java-based application named Sleuth. The Sleuth search parameters were defined as

"unipolar disorder" or "depression" in the category "Diagnosis" combined with "PET" or "fMRI" in the category "imaging modality". Furthermore we searched the reference list of identified articles and several reviews. Although some fMRI studies were reviewed and discussed, they were not included in the meta-analysis as there were only four human studies available (Greicius et al., 2007; Grimm et al., 2009a,b; Walter et al., 2009). The main problem is that fMRI studies can only measure resting state activity indirectly, e.g. via the degree of negative BOLD response (NBR) (see Grimm et al., 2009a; Walter et al., 2009), and this is complicated by the fact that NBR is not exclusively found in the resting state. In contrast, PET studies provide a direct measure of resting state in an absolute, quantifiable, way. We henceforth refrained from including the fMRI studies in our meta-analysis although a comparison to other studies was subsequently undertaken.

We then individually screened all the articles for the presence of Talairach or Montreal Neurological Institute (MNI) coordinates and tabulated the reported regional foci. We focused on studies that directly compared disordered adult patients and controls; only those reporting regional foci with the contrasts MDD > con-controls or controls > MDD were considered (see Appendix A for a list of studies).

Neurochemical abnormalities and biochemical metabolism have been investigated in human neuroimaging predominantly with magnetic resonance spectroscopy (MRS). The advantage of MRS is that it is done in the resting state so that the results are directly comparable to the above-mentioned studies in both humans and animals. One drawback is that MRS is rather difficult to conduct in subcortical regions, limiting the animal–human comparison to cortical regions. In order to account for this limitation and the wider spectrum of data available in the animal literature, neurochemical results from human postmortem studies in MDD that are carried out in subjects without recent pharmacological exposures were considered. It should be noted, however, that the postmortem brain is not in a true resting state and that interpretations of neurochemical measurements are difficult due to multiple issues (e.g. increases in GABA concentration following death)—one reason why postmortem studies can be highly variable (Knorle et al., 1997). Furthermore, given the information available, we have focused predominantly on those resting state regions that showed hyperactivity.

Since the number of MRS and postmortem studies is rather low, we have described the main results without conducting a quantitative meta-analysis. Search words in PubMed were "MRS", "spectroscopy", "postmortem", "suicide", "depression", and "MDD".

2.1.2. Exclusion criteria

Studies including depressed patients in remission or a euthymic state, subjects undergoing additional therapy (e.g. those involving medication, sleep deprivation or behaviour therapy), patients with volumetric abnormalities or brain injuries, patients with additional disorders like Alzheimer's disease, schizophrenia, borderline disorder, and obsessive–compulsive disorder were excluded. A large number of studies were excluded due to the absence of coordinates and/or designs that did not include specific comparisons relevant to the current analysis.

2.1.3. Activation likelihood estimation (ALE) meta-analysis

ALE analysis, described by Turkeltaub (Turkeltaub et al., 2002) and Laird (Laird et al., 2005), was performed with a Java-based version of ALE software named GingerALE developed by the Research Imaging Center (http://www.brainmap.org/ale). Each imported focus was modelled as localization probability distributions centered at the given coordinates. We calculated the probability that each focus was located within a particular voxel using a 3D Gaussian function of 10 mm full-width half-maximum (FWHM). The ALE value was computed as the union of these probabilities in order to create a whole-brain ALE map. Next, we performed a permutation test of randomly distributed foci to determine the statistical significance. Using the FWHM value and number of foci from each respective dataset, five thousand permutations were computed. The test was corrected for multiple comparisons using the false discovery rate (FDR) method with a threshold at $p = 0.05$. An additional cluster threshold of 400 mm^3 (50 voxels) was applied. Anatomical labels of cluster locations were provided by the Talairach Daemon. The analysis was performed with the following datasets: [MDD > controls] with coordinates from resting state studies and [controls > MDD] with coordinates from resting state studies.

2.2. Regional changes and neurochemical modulation of resting state activity in animals

2.2.1. Literature search

We aimed to identify all brain areas that have revealed an altered metabolism in the various animal models of depression based on a PubMed analysis of the literature. The search included the keywords "depression", "anhedonia", "learned helplessness", "animal", "metabolism", "c-fos", "brain", and several brain structures such as "prefrontal cortex", "perigenual anterior cingulate cortex", "hippocampus" and others (see Tables 1b and 3 for the exact regions). Due to lack of methodological instruments, absence of precise standardized coordinates systems, the wide range of experimental procedures, and the diversity of regional anatomy in different species, we were not able to conduct the same rigorous meta-analysis in animals as in humans.

Since there are no relevant PET or fMRI studies in animals (except for the study by Jang et al., 2009 noted in Tables 1b and 2b), we looked at the following indexes of animal brain metabolism: c-Fos or Fos-like expression, Fos B/delta Fos B expression, quantitative cytochrome oxidase, and [^{14}C]-2-deoxyglucose. Each of these indexes has previously been related to increased neural activity or metabolism. Considering the broad the spectrum of animal models of depression (e.g. chronic stress, bulbectomy, genetic selection, social defeat etc.), we looked at all those data that report differences in brain metabolism between depressive and normal animals. We then selected all those areas where differences in resting state metabolism turned out to be statistically significant (see Table 1b for the hyperactive structures and Table 2b for hypoactive structures).

We carried out a descriptive analysis of neurochemical GABA and glutamate anomalies within those neural structures showing altered metabolism in animal models of depression. The areas investigated were those reported in Tables 1b and 2b.

With regard to these neurochemistries, we first considered data from altered transmission/sensitivity or modified receptor expression with regard to glutamate/GABA in all those brain regions that were shown to be abnormal in the resting state condition as revealed in our first analyses. Secondly, we included data showing evidence of changes in GABAergic and glutamatergic transmission as induced by antidepressant treatment in those regions identified in the resting state analysis. Thirdly, we included data from animal studies that applied glutamate or GABA modulating drugs into the resting state regions to induce pro- or anti-depressant effects on behaviour.

2.2.2. Exclusion criteria

Studies involving adolescent animals and exposure to drugs of abuse were excluded (although appropriate non-drug-exposed controls were included), to avoid confounding issues related to neurodevelopment and drug interactions and/or drug-induced

changes in brain structure or function unrelated to the depressive-like phenotype.

In order to compare abnormal resting state activity in human and animal data, we listed the respective regions for both species and checked for hyper- and hypoactivity. Any comparison between human and animal data raises the question of homology of brain regions. Since they show analogous anatomy and are described by similar names, analysis of subcortical regions do not raise the problem of homology (see also Panksepp, 1998). In contrast, the issue of homology becomes more problematic in the case of cortical regions that show both anatomical and terminological differences between humans and animals. Nonetheless, even areas which may be considered largely 'higher-order' or evolutionarily more recent, such as the prefrontal cortex, may show strong structural and functional homologies between primates and other mammals, such as rodents (Dalley et al., 2004; Heidbreder and Groenewegen, 2003). Concerning cortical regions, we relied on criteria of homology as established by recent authors (Ongur and Price, 2000; Shumake and Gonzalez-Lima, 2003; Vertes, 2006).

3. Results

3.1. Regional hyperactivity in the resting state in humans and animals

3.1.1. Humans

Our meta-analysis revealed that MDD patients showed significantly higher resting state activity in the following regions when compared to healthy subjects: PACC, ventromedial prefrontal cortex (VMPFC), thalamic regions including the pulvinar and the dorsomedial thalamus (MDT), pallidum/putamen, and midbrain regions including VTA/SN and PAG/tectum (see Fig. 1 and Table 1a).

3.1.2. Animals

The findings of the various studies are specified in Table 1b; these are organized by dependent measure (i.e. indices of brain metabolism), depression models used (e.g. like social defeat, forced-swimming or uncontrollable shock), and species.

Different indexes of neural activity revealed the presence of a wide set of hyperactive structures in the resting states of animals with depressive-like symptoms. Overall, the neural areas showing

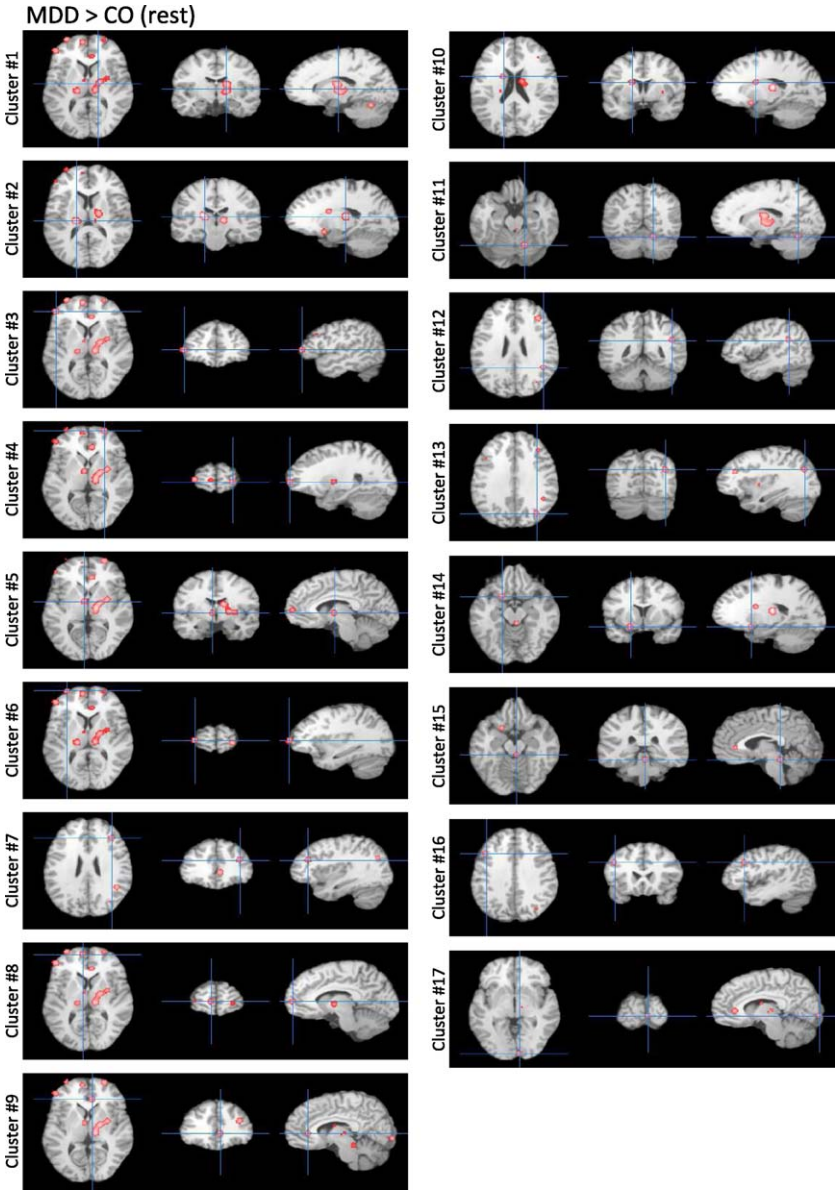

Fig. 1. Resting state hyperactivity in humans revealed by ALE analysis [MDD > Co]. See Table 1a for corresponding data. MDD = major depressive disorder; Co = controls.

Table 1a
Resting state hyperactivity in humans revealed by ALE analysis [MDD > Co].

Cluster	Volume mm^3	Weighted center			Extrema				Region	BA
		X	Y	Z	Value	X	Y	Z		
1	3520	16.92	−12.95	7.12	0.0073	18	−14	14	Thalamus	
					0.0071	20	−10	4	Lateral globus pallidus	
					0.0066	30	−4	4	Putamen	
2	976	−16.96	−24.36	11.19	0.0086	−18	−24	12	Thalamus	
3	416	−47.26	41.18	6.04	0.0063	−46	42	6	Inferior frontal gyrus	46
4	376	25.16	59.09	2.84	0.0061	24	58	2	Superior frontal gyrus	10
					0.0061	24	60	4	Middle frontal gyrus	10
5	336	−4.87	−7.16	1.91	0.0063	−4	−8	2	Thalamus	
6	336	−30.91	59.77	6.92	0.0063	−30	60	6	Superior frontal gyrus	10
					0.0063	−30	60	8	Middle frontal gyrus	10
7	328	35.9	32.03	24.25	0.0066	36	32	24	Middle frontal gyrus	9
8	312	−7.15	55.16	6.22	0.0063	−8	56	6	Medial frontal gyrus	10
9	304	6.95	31.83	3.8	0.0066	6	32	4	Anterior cingulate	24
10	304	−16	0.67	18.99	0.0065	−16	0	18	Caudate	
11	288	16.04	−61.92	−20.14	0.0066	16	−62	−20	Posterior lobe	
12	280	44	−48.1	24.44	0.0066	44	−48	24	Superior temporal gyrus	13
13	280	34.01	−71.83	28.13	0.0066	34	−72	28	Superior occipital gyrus	19
14	272	−18.23	7.85	−14.01	0.0066	−18	8	−14	Inferior frontal gyrus	47
15	264	3.94	−35.76	−15.97	0.0066	4	−36	−16	Culmen	
16	256	−42.2	18.18	32.05	0.0066	−42	18	32	Middle frontal gyrus	9
17	216	7.93	−93.82	−3.93	0.0066	8	−94	−4	Lingual gyrus	17

See Fig. 1 for corresponding images. MDD = major depressive disorder; Co = controls; BA = Brodmann areas.
Results of ALE analysis [MDD > Co] (resting state).

hyperactivity in animals with depressive-like symptoms are the anterior cingulate cortex (ACC), anterior olfactory nucleus (AON), the central nucleus of the amygdala (CeA) and the basolateral amygdala (BLA), bed nucleus of the stria terminalis (BNST), claustrum, dorsal raphe (DR), habenula (Hab), hippocampus (Hipp), hypothalamus (Hyp), infralimbic cortex (IL Cx), locus coeruleus (LC), medial preoptic area (mPOA), nucleus accumbens (Nacc), nucleus of the solitary tract (NST), paraventricular nucleus of the thalamus (paraV-Th), periaqueductal grey (PAG), piriform cortex (Pir Cx) and prelimbic cortex (PL Cx).

3.1.3. Comparison between human and animal findings

After having selected all the structures showing significantly different metabolism in animal models of depression and in human depression, we compared the findings between the two species (see above the discussion of the problem of homology) and considered possible overlapping regions as well as areas that showed abnormal metabolism in only humans or animals.

We observed corresponding resting state hyperactivity in the PACC, MDT, the VTA/SN, the PAG/Tectum, the premotor cortex and the pallidum/putamen. Hyperactivity in the AON, BNST, claustrum, DR, Pir Cx, Hab, Hipp, Hyp, LC, mPOA, NST, and the VS/Nacc, was observed only in animal models (see Table 1b). This may have been partly due to the higher anatomical resolution, especially of small subcortical nuclei, that can be obtained with the direct histological measures that can be employed in animal models.

3.2. Regional hypoactivity in the resting state in humans and animals

3.2.1. Humans

MDD patients showed significantly lower resting state regions when compared to healthy subjects in the bilateral anterior insula, the posterior cingulate cortex (PCC) and adjacent precuneus/cuneus, the bilateral superior temporal gyrus, the caudate, the left dorsolateral prefrontal cortex (DLPFC), and the supragenual anterior cingulate cortex (SACC) (see Fig. 2 and Table 2a).

Table 1b
Resting state hyperactivity in animal models of depression.

Ref	Model	Species	Measure	Brain regions
Beck and Fibiger (1995)	Chronic stress	Rats	c-fos	ACC, AON, CeA, claustrum, dentate gyr, Pir Cx, dorsopeduncular Cx, IL Cx, septum, occipital Cx, Hyp, supramammillary area, ParaV-Thal, pontine n.
Matsuda et al. (1996)	Chronic stress	Mice	c-fos	Amyg, Hipp, Hyp, septum, LC, NST
Nikulina et al. (1998)	Social defeat	Mice	fos-LI	BLA, CeA, DR, IL Cx, LC, MeA, Nacc, PL Cx, VTA
Miczek et al. (1999)	Social defeat	Mice	c-fos	Ventrolateral PAG
Shumake et al. (2003)	Genetic	Rats	Quantitative cytochrome oxidase	Habenula, Hipp, IL Cx, ParaV-Hyp, PL Cx
Huang et al. (2004)	Learned helplessness	Mice	c-fos	ParaV-Hyp
Greenwood et al. (2005)	Learned helplessness	Rats	c-fos	BNST, habenula
Lino-de-Oliveira et al. (2006)	Forced swim test	Rats	fos-LI	PAG
Frank et al. (2006)	Social defeat; genetic	Rats	c-fos	CeA, MeA, medial preoptic area, ParaV-Hyp
Berton et al. (2007)	Learned helplessness	Mice	Delta FosB	Ventrolateral PAG
Frenois et al. (2007)	LPS immune induction	Rats	FosB/Delta FosB	BNST, Hyp, ParaV-Thal, NST
Kroes et al. (2007)	Social defeat	Rats	ACh gene express.	PAG
Stone et al. (2007)	Various	Mice	c-fos	Anterior Pir Cx, Cg gyr, Nacc, secondary motor Cx
Jang et al. (2009)	Forced swim test	Rats	[^{18}F] FDG PET	Cerebellum, motor/sensory Cx

ACC, anterior cingulate cortex; ACh, acetylcholine; Amyg, amygdala; AON, anterior olfactory nucleus; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; Cg, cingulate; Cx, cortex; DR, dorsal raphe; gyr, gyrus; Hipp, hippocampus; Hyp, hypothalamus; IL, infralimbic; MeA, medial nucleus of the amygdala; Nacc, nucleus accumbens septi; PAG, periaqueductal grey; ParaV-Hyp, paraventricular nucleus of the hypothalamus; ParaV-Thal, paraventricular nucleus of the thalamus; Pir, piriform; PL, prelimbic; LC, locus coeruleus; NST, nucleus of the solitary tract; VTA, ventral tegmental area.

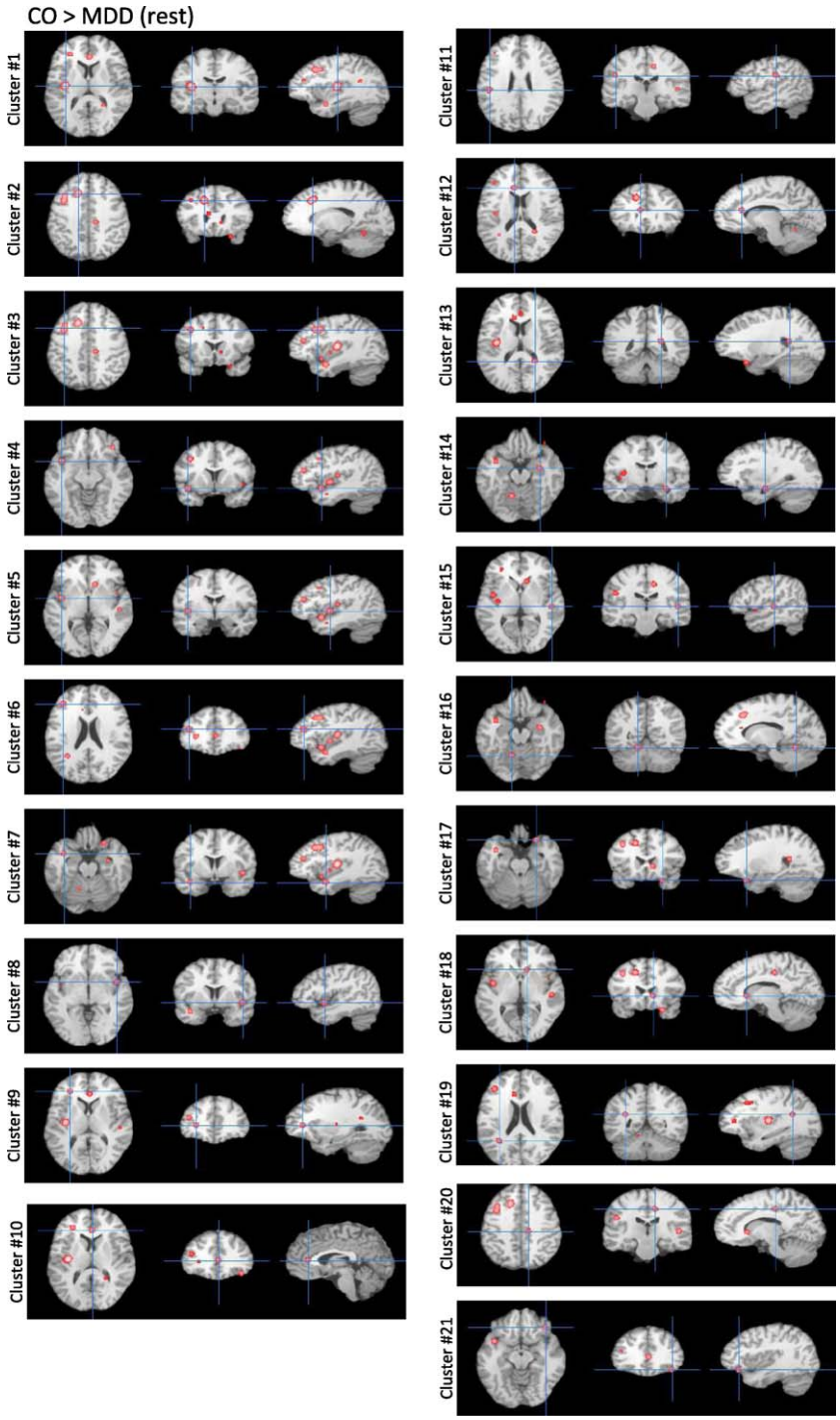

Fig. 2. Resting state hypoactivity in humans revealed by ALE analysis [Co > MDD]. See Table 2a for corresponding data. MDD = major depressive disorder; Co = controls.

3.2.2. Animals

Evidence of hypoactive structures in the resting state of animal models of depression are sparse (see Table 2b). This may, in part, be due to the fact brain changes in animal models of depression are often measured soon after the application of discrete stressors. Congenitally helpless rats have shown decreased metabolism in the caudate in the SACC and in the DMPFC (Shumake et al., 2003). Bulbectomized rats also presented decreased [^{14}C]-2-deoxyglucose metabolism in the CP (Skelin et al., 2008). The other findings that have reported indexes of hypoactivity are not consistent or are contradicted by other results.

3.2.3. Comparison between human and animal findings

Hypoactivity in the resting state was observed in both animals and humans in the SACC, the left lateral prefrontal cortex including the DLPFC, and the caudate (see Table 3). While hypoactivity in the bilateral anterior insula and the bilateral superior temporal gyrus have, to date, been observed only in humans (see Table 3).

3.3. Glutamatergic modulation of resting state activity in humans and animals

We investigated glutamatergic abnormalities in those regions that showed abnormal resting state activity thereby focusing

Table 2a
Resting state hypoactivity in humans revealed by ALE analysis [Co > MDD].

Cluster	Volume (mm^3)	Weighted center			Extrema				Region	BA
		X	Y	Z	Value	X	Y	Z		
1	1104	−34.18	−16.9	9.92	0.0101	−34	−16	10	Claustrum	
2	984	−14.79	21.06	38.09	0.0087	−16	20	38	Cingulate gyrus	32
3	928	−35.56	12.76	38.3	0.0072	−36	10	38	Precentral gyrus	9
4	384	−39.45	7.05	−10.31	0.0066	−40	8	−10	Sub-lobar	13
5	368	−39.89	−5.98	0.22	0.0066	−40	−6	0	Insula	13
6	352	−37.78	34	19.74	0.0066	−38	34	20	Middle frontal gyrus	46
7	336	−36.29	0.34	−19.52	0.0067	−36	0	−20	Superior temporal gyrus	38
8	336	43.81	2.15	−4.22	0.0066	44	2	−4	Insula	13
9	336	−27.06	35.63	7.36	0.0064	−26	36	8		
10	328	2.77	31.16	9.27	0.0062	2	30	10	Anterior cingulate	24
11	320	−46.07	−27.74	24.35	0.0066	−46	−28	24	Inferior parietal lobule	40
12	312	−8.16	24.81	15.96	0.0065	−8	26	16	Anterior cingulate	24
13	296	23.12	−48.06	13.26	0.0063	22	−48	12	Posterior cingulate	23
14	288	30.64	−11.11	−16.98	0.0061	32	−10	−16	Parahippocampal gyrus, hippocampus	36
15	288	48.78	−25	2.78	0.0061	48	−26	2	Superior temporal gyrus	22
					0.0061	48	−26	4	Superior temporal gyrus	41
16	280	−11.82	−57.53	−16.67	0.0063	−12	−58	−18	Declive, culmen	
17	272	25.27	17.47	−22.16	0.0065	26	18	−22	Inferior frontal gyrus	47
18	264	10.7	17.02	1.19	0.0065	10	18	0	Caudate	
19	264	−30.97	−52.92	18.77	0.0063	−32	−54	18	Superior temporal gyrus	22
					0.0063	−30	−54	18	Middle temporal gyrus	39
20	264	12.24	−25.81	39.95	0.0066	12	−26	40	Cingulate gyrus	31
21	256	37.91	30.1	−12.15	0.0066	38	30	−12	Inferior frontal gyrus	47

See Fig. 2 for corresponding images. MDD = major depressive disorder; Co = controls; BA = Brodmann areas.
Results of ALE analysis [Co > MDD] (resting state).

predominantly on hyperactive resting state regions (see Tables 1a, 1b and 3).

3.3.1. Humans

In summary, human results from MRS, fMRI/PET, postmortem, and pharmacological studies provide evidence for glutamatergic abnormalities in anterior ventral midline regions.

3.3.2. Animals

In summary, animal data show increased total concentration and transmission of glutamate in several regions that showed metabolic hyperactivity in the resting state. One should however note that some studies also show decreased total glutamate concentration in PFC and/or Hipp. In contrast to the glutamate concentration data, animal results are consistent with regard to glutamatergic receptors showing increased NMDA receptor and decreased AMPA receptor sensitivity/expression in hyperactive resting state regions like PACC/VMPFC, VS, putamen, and MDT (and DLPFC) (see Table 3). It should be noted that similar glutamate anomalies were seen also in neural structures outside of the ventral anterior midline regions, for example the Amyg, the Hyp, the DR, the VS/NACC and the SN/VTA.

3.3.3. Comparison between humans and animals

Data in humans indicate lower glutamate total concentrations in hyperactive ventral anterior cortical midline regions like the PACC and VMPFC (see Table 3). Decreased glutamate concentrations in humans contrast with the findings in animals that show rather increased glutamate concentrations in cortical (and subcortical) regions. One should however note that human findings are only based on the PACC/VMPFC while animal findings highlight predominantly subcortical (and some cortical) regions. Furthermore, it should be noted that the animal data are not fully consistent with some studies showing decreased glutamate concentrations (see Table 3).

In contrast to the data regarding glutamate concentrations, the animal data on NMDA and AMPA receptors are fully consistent with what may be pharmacological and biochemically inferred from the human data. Studies show increased NMDA receptors and decreased AMPA receptor expression/sensitivity in hyperactive resting state regions like PACC/VMPFC, VS, putamen, MDT, hippocampus/amygdala (and DLPFC) (see also Fig. 3). Unfortunately, there are no comparable data available on NMDA and AMPA receptors in humans (see Table 3).

3.4. GABAergic modulation of resting state activity in humans and animals

3.4.1. Humans

In summary, human findings provide some evidence for altered GABAergic metabolism in cortical regions, though the results remain controversial and require further investigation.

3.4.2. Animals

In summary, animal data show consistent findings of decreased total GABA concentration and synthesis and decreased $GABA_{A/B}$ receptor sensitivities/expression in hyperactive resting state

Table 2b
Resting state hypoactivity in animal models of depression.

Ref	Model	Species	Measure	Brain regions
Caldecott-Hazard et al. (1988)	Various	Rats	[^{14}C]-2 deoxyglucose	Secondary motor Cx
Persico et al. (1995)	Chronic stress	Rats	c-fos	PFC
Shumake et al. (2003)	Genetic	Rats	Quant cyto oxidase	ACC, anterior Pir Cx, BNST, caudate-putamen, DMPFC, septum, VP, VTA
Huang et al. (2004)	Learned helplessness	Mice	c-fos	Dentate gyrus, lateral septal n.
Skelin et al. (2008)	Bulbectomy	Rats	[^{14}C]-2 deoxyglucose	Caudate-putamen
Jang et al. (2009)	Forced swim test	Rats	[^{18}F] FDG PET	Hipp, IC, left insula, left amyg

DMPFC, dorsomedial prefrontal cortex; IC, inferior colliculus; PFC, prefrontal cortex; see Table 1b for additional abbreviations.

Table 3
Resting state hyperactivity and glutamate- and GABAergic function in animal and human depression.

Brain regions	Human brain activity	Animal brain activity	Human Glx levels	Human Glu receptors	Animal Glu levels	Animal Glu receptors	Human GABA levels	Human GABA receptors	Animal GABA levels	Animal GABA receptors	Neurochemical-related references
Amyg (right)	–	Up	–	–	–	High/low NMDA	–	–	Down	–	Ho et al. (2001), Seidel et al. (2008)
AON	–	Up	–	–	–	–	–	–	–	–	–
BNST	–	Up	–	–	–	–	–	–	Down	–	Bowers et al. (1998)
Claustrum	–	Up	–	–	–	–	–	–	–	–	–
DLPFC/PL	Up	–	Down (MR)	–	Up/down	High NMDA; low AMPA; low GluR2	Normal (MR); Down (PM)	–	Down	High/low GABA-A; low GABA-B	Acosta et al. (1993), Dennis et al. (1993), Hasler et al. (2007), Li et al. (2008), Michael-Titus et al. (2008), Sartorius et al. (2007)
DMPFC	–	Up/down	Down (MR)	–	Up/down	High NMDA; low AMPA; low GluR2	Normal (MR)	-	Down	High/low GABA-A; low GABA-B	Acosta et al. (1993), Dennis et al. (1993), Hasler et al. (2007), Li et al. (2008), Michael-Titus et al. (2008), Webster et al. (2000)
DR	–	Up	–	–	Up/down	High NMDA	-	–	–	–	
Hab	–	Up	–	–	–	–	–	–	–	–	
Hipp	–	Up	Down (MR)	–	Up/down	High NMDA; high/low mGlu5	Down (PM)	–	Down	High/low GABA-A; low GABA-B	Block et al. (2009), Cullinan and Wolfe (2000), Drugan et al. (1989), Duncko et al. (2003), Gronli et al. (2007), Joels et al. (2004), Li et al. (2008), Sartorius et al. (2007), Wieronska et al. (2001)
Hyp	–	Up	–	–	Up	–	–	–	Down	Low GABA-A	Acosta et al. (1993), Cullinan and Wolfe (2000), Herman et al. (2008)
LC	–	Up	–	–	–	–	–	–	–	–	
MDT/thalamus	Up	Up	–	–	–	High NMDA	–	–	–	–	Robichaud et al. (2001); see Table 1a
mPOA	–	Up	–	–	–	–	–	–	–	–	
NTS		UP	–	–	–	–	–	–	–	–	
Occ Cx			Normal/up (MR)				Down (MR)				Bhagwagar et al. (2007), Sanacora et al. (2004)
PACC	Up	Up	Down (MR; Gln only)	–	–	High NMDA	Normal (MR, PM)	–	–	–	Auer et al. (2000), Sartorius et al. (2007), Walter et al. (2009); see Table 1a
PAG/Tectum	Up	Up	–	–	–	–	–	–	–	–	See Table 1a
Pallidum	Up	Up	–	–	–	–	–	–	–	–	See Table 1a
Pir Cx	–	Up	–	–	–	–	–	–	–	–	
Pulvinar	Up	–	–	–	–	–	–	–	–	–	See Table 1a
Putamen	Up	Up	–	–	–	High NMDA; low AMPA	–	–	Down	Low GABA-A	Acosta et al. (1993), Drugan et al. (1989); see Table 1a
Septum	–	Up/down	–	–	–	–	–	–	Down	High GABA-A	Kram et al. (2000)
VMPFC/IL	Up	–	Down (MR)	–	Up/down	High NMDA; low AMPA	–	–	Down	High/low GABA-A; low GABA-B	Acosta et al. (1993), Dennis et al. (1993), Hasler et al. (2007) Li et al. (2008), Sartorius et al. (2007), Webster et al. (2000); see Table 1a
VS/NACC	–	Up	–	–	–	High NMDA; low AMPA	–	–	Down	–	Borsini et al. (1988), Duncko et al. (2003)
VTA/SN	Up	Up/down	–	–	–	High/low NMDA	–	–	–	–	Duncko et al. (2003), Fitzgerald et al. (1996); see Table 1a

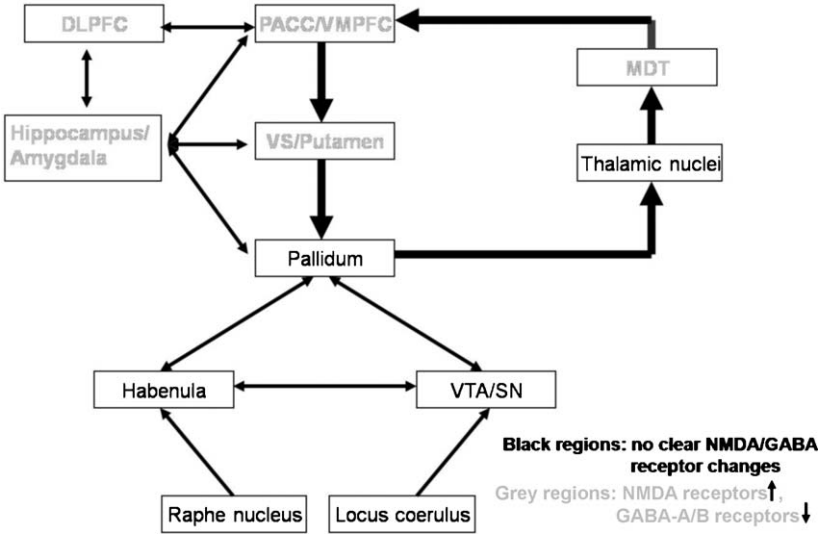

Fig. 3. Glutamat- and GABAergic modulation of resting state hyperactivity in a ventral anterior cortico-subcortical–cortical reentrant circuit (thick arrows). DLPFC = dorsolateral prefrontal cortex; MDT = mediodorsal thalamus; PACC = pregenual anterior cingulate cortex; SN = substantia nigra; VTA = ventral tegmental area.

regions such as the PACC/VMPFC, VS, putamen, MDT, hippocampus/amygdala and DLPFC (see Table 3). Other areas outside the ventral anterior midline regions that also have shown similar abnormalities are the Hyp, and the VS/NACC.

3.4.3. Comparison between humans and animals

While there is only modest evidence investigating GABA concentrations in humans, animal data have consistently shown decreased total GABA concentration in most of the cortical and subcortical structures that are metabolically hyperactive during depressive states. Moreover, the animal data support decreased $GABA_{A/B}$ receptor expression/sensitivity in various cortical and subcortical regions (VS, putamen, PACC/VMPFC, MDT, hippocampus/amygdala, DLPFC) that show hyperactivity in the resting state (see Table 3).

4. Discussion

This study investigated the functional anatomy and neurochemical modulation of resting state activity using a cross-species translational approach. A direct comparison was made between the human data (using a meta-analysis of studies involving patients with MDD), and the animal data (investigating anatomical, biochemical, and pharmacological changes and manipulations in models of depression). The main results of our translational analysis are as follows. First, we observed resting state hyperactivity in a common set of regions in both animals and humans that concern predominantly ventral anterior midline regions like PACC, the VMPFC, the VS, and the MDT. These hyperactive regions must be distinguished from more dorsal posterior midline regions that show hypoactivity in the resting state in both animals and humans. Second, hyperactive resting state regions tend to show abnormal glutamatergic metabolism with reduced glutamate levels (humans) as well as increased NMDA and decreased AMPA receptor density/sensitivity (animals). Animal findings also suggest decreased GABA concentrations and decreased $GABA_{A/B}$ receptor expression/sensitivities in these hyperactive regions.

Taken together, our translational analysis suggests that abnormal hyperactivity in the resting state may be related to abnormal glutamatergic and GABAergic metabolism in depression. This not only sheds light on the abnormal resting state activity in depression but also on the neurochemical modulation of the default-mode network as shared among humans and animals. In addition, it is interesting to note that these neuroanatomical and biochemical consistencies across both animals and humans provide evidence for the use of an abnormal resting state as a possible biological endophenotype of depression—as imaging techniques such as fMRI, PET, and MRS are increasingly demonstrating the potential to provide a bridge from the clinical to the basic mechanism level (Hasler et al., 2004). More specifically, we suggest that high resting state activity in default-mode network regions (as mediated by alterations in GABA and glutamate) may be a potential endophenotype of depression and may also account for the increased self-focus observed (Grimm et al., 2009b). Such high resting state activity, including its biochemical and psychopathological manifestations, may distinguish depression from other psychiatric disorders such as schizophrenia or anxiety disorders. However, despite its cross-species biological, and clinical plausibility, the assumption of high resting state activity as a possible endophenotype needs to be further substantiated, especially with regard to underlying genetic changes.

4.1. Resting state hyper- and hypoactivity

To summarize, our first aim was to investigate resting state activity in both humans and animals. Early PET studies in human MDD observed increased resting state activity predominantly in ventral anterior cortical midline regions like the PACC and the VMPFC (see Mayberg, 2002, 2003; Phillips et al., 2003 for reviews). The assumption of abnormalities in resting state regions was further corroborated by recent findings of abnormalities in the ventral regions of the default-mode network in human MDD (Greicius et al., 2007; Grimm et al., 2009a). Our meta-analysis of resting state studies in human MDD confirms abnormal resting state hyperactivity in ventral cortical midline regions like the PACC and the VMPFC (see also Fitzgerald et al., 2007 who observed similar regions). It is important to note that while there are limitations to the ALE method compared to other approaches, as discussed elsewhere (Wager et al., 2009), the current meta-analysis results are in accord with the results described. The ALE technique has been employed in several meta-analyses (see Brown et al., 2005; Owen et al., 2005, for more see www.brainmap.org/pubs) including in MDD (Fitzgerald et al., 2006). Though ALE has some weakness in methodological terms because it is coordinate-based, a recent study comparing different meta-analytic programs

yielded similar results for ALE and other coordinate-based and image-based programs (Salimi-Khorshidi et al., 2009).

Interestingly, we observed that many regions, similar to those found in the human studies, showed hyperactivity in the resting state in animal models of depression. Concordant findings were evident in cortical regions like the PACC and the VMPFC as well as subcortical regions like the MDT, pallidum, putamen, VTA/SN, and the midbrain. Animal studies also revealed hyperactivity in more discrete subcortical regions like the locus coerulus, raphe nucleus, Hab, BNST, solitary tract, and the septum, all of which, due to low spatial resolution, cannot be readily imaged in humans. This fact raised the question of whether such hyperactive subcortical loci may also be considered part of the ventral anterior midline regions. Alternatively, it is likely that these subcortical areas both modulate and are modulated by ventral anterior midline regions. Regardless, strong reciprocal connectivity between hyperactive subcortical areas and those belonging to ventral anterior midline regions has been strongly supported in animal studies (Gabbott et al., 2005; Hoover and Vertes, 2007; but see also Stone et al., 2008). Taken together, these translational data suggest resting state hyperactivity across species in ventral anterior midline regions like PACC, VMPFC, VS, putamen and MDT in depression.

What remains unclear though is how resting state hyperactivity in these ventral anterior midline regions translate into behaviour, e.g., depressive symptoms. Stone et al. (2007, 2008) associate these ventral regions with a neural circuit involved in the organization of the stress response. Many of these regions have also been associated with the Behavioral Inhibition System (BIS) by Gray (1994) and various other negative affective systems (Panksepp, 1998). The BIS is proposed to regulate avoidant behaviour, inhibition of behaviour, anxiety, negative affective states and neuroticism. In more refined studies of emotional systems, it is clear that the higher reaches of various emotional systems, especially those related to social processes such as separation distress and pro-social behaviours such as maternal nurturance and play, are also concentrated in these regions of the brain (Panksepp, 1998). Our translational findings suggest that various negative/emotional stress systems, however they are conceptualized, are hyperactive in depression; this is in accord with clinical symptoms, behaviour, and personality-related characteristics in MDD patients. However, the specific types of emotional/stress systems that are most affected in depression needs to be addressed in future translational studies. Furthermore, one might consider that ventral anterior midline regions have also been associated with self-relatedness in healthy humans (Northoff and Bermpohl, 2004; Northoff et al., 2006; Northoff and Panksepp, 2008). This may lead one to speculate that abnormal resting state hyperactivity may be related to the ruminations, with an increased, affectively negative self-focus, often observed in clinically depressed patients (Northoff, 2007). Though there is currently little direct support for this conjecture, there is at least one study that relates the MDD patients' increased self-focus to abnormal activity in anterior midline regions (Grimm et al., 2009b).

In contrast to hyperactive regions, regions that were hypoactive were located more dorsally and posterior—such as the SACC and the PCC (and might be deemed to be more cognitive regions of the forebrain). However, it should be emphasized that at the present time the regional overlap between findings in animals and humans is not as consistent and clear-cut as it is for the more ventral hyperactive regions, including various subcortical regions long implicated in emotionality in animal studies (Panksepp, 1998). In sum, the translational findings show a stronger and more consistent convergence between animal and human data with respect to the hyperactive resting state regions than those showing hypoactivity. Because of this, we have concentrated on the pathophysiological mechanisms of the hyperactive resting state regions.

4.2. Resting hyperactivity and glutamatergic and GABAergic modulation

The second main aim of our translational analysis was to investigate the relationship between abnormal resting state activity and neurochemical parameters, with a focus on glutamate and GABA. Recent studies in human MDD have demonstrated a potential glutamatergic mechanism as indicated by the antidepressant effects of the NMDA receptor antagonist ketamine and some AMPA agonists (Bleakman et al., 2007; Chourbaji et al., 2008; Maeng and Zarate, 2007; Maeng et al., 2008). Spectroscopic findings showed reduced glutamate in the PACC in human MDD (Auer et al., 2000; Berman et al., 2000; Hasler et al., 2007; Northoff et al., 1997, 1999; Walter et al., 2009; Zarate et al., 2006). Importantly, the spectroscopic findings were obtained in the resting state raising the question of whether this abnormal resting state hyperactivity may be due to abnormal glutamatergic metabolism in depression.

If resting state hyperactivity in human PACC is indeed due to abnormal glutamatergic metabolism, one would also expect abnormal expression/sensitivity of glutamatergic receptors (e.g. NMDA and AMPA receptors). Consistent with this possibility, animal studies report predominant increases in NMDA, and decreases in AMPA, receptor sensitivity/expression as well as reduction of NMDA receptors by antidepressant treatment in certain resting state regions (see Fig. 3). These observations are in accord with the effects of ketamine on functional PACC activity and therapeutic effects in human depression (Northoff et al., 1997, 1999; Salvadore et al., 2009; Zarate et al., 2006). Ketamine antagonizes the NMDA receptor hyperfunction (as observed in animals) and may thereby reduce the abnormally increased neural excitation that contributes substantially to resting state hyperactivity in regions like PACC, VMPFC, VS, putamen, and MDT (see Fig. 3). Hence, while there seems to be convergence between human and animal data, future investigation of NMDA receptors in human depression are needed to further corroborate our assumption of the linkage between NMDA receptor hyperfunction and increased resting state activity.

One may question how the reduced PACC glutamate concentration in human depression may be related to resting state hyperactivity and NMDA receptor hyperfunction in the same region (and others), as observed in animals. A recent study (Walter et al., 2009) demonstrated that an fMRI marker of possible resting state hyperactivity in the PACC (i.e. decreased negative BOLD response (NBR)), correlated abnormally with the concentration of glutamate in the same region in depressed patients. In contrast, we did not observe this correlation in healthy subjects suggesting that their resting state activity was not directly regulated by glutamate (but may perhaps be regulated by GABA)—although, as discussed in Northoff (2007) , it is important to note the possibility that the excitation-inhibition balance producing NBR may be related to glutamatergic input. These results support our proposal of glutamatergic mediation of resting state hyperactivity in the PACC. Future studies in human depression are needed to investigate the relationship between glutamate and NBR during challenge with an NMDA antagonist, such as ketamine, which may reduce resting state hyperactivity (which may reflect attenuation of negative affective arousal) by decoupling it from overactive glutamatergic influences that promote negative affect. Parallel animal studies may provide the opportunity to test the impact of locally applied NMDA receptor agonists and antagonists on PACC (and other regions') resting state activity in both normal and depressive-like states.

In addition to glutamatergic abnormalities, GABAergic metabolism may also be involved in resting state hyperactivity. Though some human studies (e.g. MRS; postmortem) show reduced GABA concentration, one has to take into account the low number of studies and the variability of existing results. In contrast to human findings, a more coherent picture emerges from the animal data. These data show reductions in both GABA concentrations and $GABA_{A/B}$ receptor sensitivity/expression in various hyperactive resting state regions, including the PACC/VMPFC, VS, putamen, and MDT (see Table 3 and Fig. 3). This is in line with the observation of the therapeutic efficacy of GABAergic agonists like lorazepam in acute depression. However, future studies are necessary to demonstrate that GABAergic drugs directly impact resting state activity in PACC and other ventral midline regions in both healthy (see Northoff et al., 2002 for one study in this direction) and depressed subjects.

These GABAergic abnormalities may be related to resting state hyperactivity in ventral anterior midline regions. In human MDD, resting state hyperactivity is indicated by reduced NBR during emotion processing (Grimm et al., 2009a). NBR have been shown in healthy humans to be related to neural inhibition and GABA (see Shmuel et al., 2002, 2006; Northoff et al., 2002; Northoff 2007). One would consequently expect that reduced NBR in human MDD may no longer be modulated by GABA which is exactly what a recent fMRI-MRS study demonstrated (Walter et al., 2009). Instead of being modulated by GABA, reduced NBRs in human MDD were related to glutamate. Hence, resting state activity in depression appears to shift from a primarily GABA-mediated modulation to a glutamate-mediated modulation.

The findings by Grimm et al. (2009a,b) and Walter et al. (2009) are very much in line with those reported recently by Sheline et al. (2009). In line with the study of Grimm et al. (2009a), Sheline et al. (2009) conducted an emotional appraisal task and observed a failure to properly deactivate in several regions of the default-mode network (including the ventromedial prefrontal cortex, the anterior cingulate, and lateral parietal cortex). This is very much in line with the findings by Grimm et al. (2009a) who also observed significantly reduced NBR in depressed patients during both emotion perception and appraisal. While both Grimm et al. (2009a) and Sheline et al. (2009) investigate emotional appraisal, another paper by Grimm et al. (2009b) directly targeted self-relatedness by investigating appraisal or judgment regarding the degree of self-relatedness. Interestingly, they observed altered neural activity in predominantly midline regions that overlapped with those showing reduced NBR. These results suggest that the reduced NBR observed in the default-mode network may be traced back psychologically to altered self-relatedness; more specifically, to an increased self-focus—as was behaviourally observed by Grimm et al. (2009b) (see also Northoff, 2007).

Overall, animal findings suggest increased expression/sensitivity in NMDA receptors while AMPA receptors and $GABA_{A/B}$ receptors seem to be decreased. This may result in a net effect of increased neural excitation and decreased neural inhibition. Such increases in neural excitation may in turn reduce the amount of NBR that, as studies in healthy subjects show (see above), strongly relies on neural inhibition. One may consequently hypothesize that resting state hyperactivity in depression may be related to the lack of GABA-mediated neural inhibition and an excess in glutamate-mediated neural excitation. This however needs to be tested in future studies focusing on electrophysiology measurements in these regions during neurochemical modulation, along with causal pharmacological studies in animal models.

Finally, while not a main focus of this review, it is important to note recent work regarding the role of various neuromodulators in the regulation of GABA and glutamate, with particular relevance to depression. Neuromodulators, in this context, include both substances other than GABA and glutamate that may modulate their activity as well as agonistic and antagonistic substances that directly modulate GABA- and glutamatergic receptors.

For instance, some neurosteroids (e.g. allopregnanolone) act as positive allosteric modulators of the $GABA_A$ receptor. There is evidence that the effects of serotonin selective reuptake inhibitors on depression may be in part related to their ability to increase neurosteroid concentrations and, thus, increase the inhibitory effects of GABA (MacKenzie et al., 2007; Pinna et al., 2006). There is also strong evidence that some neurotrophins (especially brain-derived neurotrophic factor) and neuropeptides (e.g. corticotropin-releasing factor and substance P) play a key role in the pathophysiology of depression (Nemeroff, 1996; Rakofsky et al., 2009; Thakker-Varia and Alder, 2009); their mechanism of action may include a rebalancing of amino acid neurotransmitter function (Skorzewska et al., 2009; Stacey et al., 2002a,b; Ungless et al., 2003), though much more work is needed to clarify the precise mechanisms and brain areas involved.

In addition, as the GABA and glutamate systems appear to be key in depression – although mimetic drugs tend to have many unwanted side effects – allosteric modulators of their receptors have been developed and found to be effective against some depressive symptoms. Interestingly, $GABA_B$ receptor antagonists, and both $GABA_A$ and $GABA_B$ receptor positive allosteric modulators may have antidepressant properties; although the results are largely limited to animal studies (Frankowska et al., 2007; Kalueff and Nutt, 2007). Positive allosteric modulators of AMPA and mGlu receptors also show promise in reducing depressive symptoms though, once again, there is limited data regarding humans (Black, 2005; Gasparini and Spooren, 2007). Consistent with the role of multiple neuromodulators, a promising line of antidepressant drug development and current treatment has focused on compounds that selectively target multiple systems (Millan, 2009).

4.3. Conclusion

To our knowledge, this is the first report utilizing a systematic translational approach to animal and human data with regard to depression. Regarding the pathophysiology of depression, our focus was on the anatomy and neurochemistry of resting state activity. We demonstrated that studies of animal and human depression show resting state hyperactivity primarily in midline subcortical and cortical regions. Neurochemical findings suggest that resting state hyperactivity in this loop may be related to glutamatergic abnormalities with up-regulation of NMDA receptors and down-modulation of AMPA receptors across these regions. This may lead to increased neural excitation, accompanied by negative affective/emotional arousals, which may be further enhanced by decreased neural inhibition in these regions as mediated by reduced GABA activity (and perhaps concentrations) and/or $GABA_{A/B}$ receptor expression/sensitivity. Taken together, these translational results demonstrate resting state hyperactivity in ventral anterior midline regions in depression and its modulation by abnormal glutamate- and GABAergic metabolism. This also contributes to a better understanding of the biochemical underpinnings of the resting state in the default-mode network of both animals and humans.

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Appendix A. Meta-analysis references

Bench, C.J., Friston, K.J., Brown, R.G., Scott, L.C., Frackowiak, R.S., Dolan, R.J., 1992. The anatomy of melancholia—focal abnormalities of cerebral blood flow in major depression. Psychol. Med. 22, 607–615.

Brody, A.L., Saxena, S., Stoessel, P., Gillies, L.A., Fairbanks, L.A., Alborzian, S., Phelps, M.E., Huang, S.C., Wu, H.M., Ho, M.L., Ho, M.K., Au, S.C., Maidment, K., Baxter, L.R. Jr., 2001. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy. Arch. Gen. Psychiatry 58, 631–640.

Drevets, W.C., Videen, T.O., Price, J.L., Preskorn, S.H., Carmichael, S.T., Raichle, M.E., 1992. A functional anatomical study of unipolar depression. J. Neurosci. 12, 3628–3641.

Kennedy, S.H., Evans, K.R., Krüger, S., Mayberg, H.S., Meyer, J.H., McCann, S., Arifuzzman, A.I., Houle, S., Vaccarino, F.J., 2001. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am. J. Psychiatry 158, 899–905.

Kimbrell, T.A., Ketter, T.A., George, M.S., Little, J.T., Benson, B.E., Willis, M.W., Herscovitch, P., Post, R.M., 2002. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. Biol. Psychiatry 52, 1031–1032.

MacHale, S.M., Lawŕie, S.M., Cavanagh, J.T., Glabus, M.F., Murray, C.L., Goodwin, G.M., Ebmeier, K.P., 2000. Cerebral perfusion in chronic fatigue syndrome and depression. Br. J. Psychiatry 176, 550–556.

Saxena, S., Brody, A.L., Ho, M.L., Alborzian, S., Ho, M.K., Maidment, K.M., Huang, S.C., Wu, H.M., Au, S.C., Baxter, L.R. Jr., 2001. Cerebral metabolism in major depression and obsessive–compulsive disorder occurring separately and concurrently. Biol. Psychiatry 50, 159–170.

Videbech, P., Ravnkilde, B., Pedersen, A.R., Egander, A., Landbo, B., Rasmussen, N.A., Andersen, F., Stødkilde-Jørgensen, H., Gjedde, A., Rosenberg, R., 2001. The Danish PET/depression project: PET findings in patients with major depression. Psychol. Med. 31, 1147–1158.

References

Acosta, G.B., Otero Losada, M.E., Rubio, M.C., 1993. Area-dependent changes in GABAergic function after acute and chronic cold stress. Neurosci. Lett. 154, 175–178.

Auer, D.P., Putz, B., Kraft, E., Lipinski, B., Schill, J., Holsboer, F., 2000. Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. Biol. Psychiatry 47, 305–313.

Beck, C.H., Fibiger, H.C., 1995. Chronic desipramine alters stress-induced behaviors and regional expression of the immediate early gene, c-fos. Pharmacol. Biochem. Behav. 51, 331–338.

Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 47, 351–354.

Berton, O., Covington 3rd, H.E., Ebner, K., Tsankova, N.M., Carle, T.L., Ulery, P., Bhonsle, A., Barrot, M., Krishnan, V., Singewald, G.M., Singewald, N., Birnbaum, S., Neve, R.L., Nestler, E.J., 2007. Induction of deltaFosB in the periaqueductal gray by stress promotes active coping responses. Neuron 55, 289–300.

Bhagwagar, Z., Wylezinska, M., Jezzard, P., Evans, J., Ashworth, F., Sule, A., Matthews, P.M., Cowen, P.J., 2007. Reduction in occipital cortex gamma-aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects. Biol. Psychiatry 61, 806–812.

Black, M.D., 2005. Therapeutic potential of positive AMPA modulators and their relationship to AMPA receptor subunits. A review of preclinical data. Psychopharmacology (Berl) 179, 154–163.

Bleakman, D., Alt, A., Witkin, J.M., 2007. AMPA receptors in the therapeutic management of depression. CNS Neurol. Disord Drug Targets 6, 117–126.

Block, W., Traber, F., von Widdern, O., Metten, M., Schild, H., Maier, W., Zobel, A., Jessen, F., 2009. Proton MR spectroscopy of the hippocampus at 3 T in patients with unipolar major depressive disorder: correlates and predictors of treatment response. Int. J. Neuropsychopharmacol. 12, 415–422.

Borsini, F., Mancinelli, A., D'Aranno, V., Evangelista, S., Meli, A., 1988. On the role of endogenous GABA in the forced swimming test in rats. Pharmacol. Biochem. Behav. 29, 275–279.

Bowers, G., Cullinan, W.E., Herman, J.P., 1998. Region-specific regulation of glutamic acid decarboxylase (GAD) mRNA expression in central stress circuits. J. Neurosci. 18, 5938–5947.

Brown, S., Ingham, R.J., Ingham, J.C., Laird, A.R., Fox, P.T., 2005. Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. Hum. Brain Mapp. 25, 105–117.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38.

Caldecott-Hazard, S., Mazziotta, J., Phelps, M., 1988. Cerebral correlates of depressed behavior in rats, visualized using 14C-2-deoxyglucose autoradiography. J. Neurosci. 8, 1951–1961.

Cenci, M.A., Whishaw, I.Q., Schallert, T., 2002. Animal models of neurological deficits: how relevant is the rat? Nat. Rev. Neurosci. 3, 574–579.

Chourbaji, S., Vogt, M.A., Fumagalli, F., Sohr, R., Frasca, A., Brandwein, C., Hortnagl, H., Riva, M.A., Sprengel, R., Gass, P., 2008. AMPA receptor subunit 1 (GluR-A) knockout mice model the glutamate hypothesis of depression. FASEB J. 22, 3129–3134.

Cryan, J.F., Slattery, D.A., 2007. Animal models of mood disorders: Recent developments. Curr. Opin. Psychiatry 20, 1–7.

Cullinan, W.E., Wolfe, T.J., 2000. Chronic stress regulates levels of mRNA transcripts encoding beta subunits of the GABA(A) receptor in the rat stress axis. Brain Res. 887, 118–124.

Dalley, J.W., Cardinal, R.N., Robbins, T.W., 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci. Biobehav. Rev. 28, 771–784.

Dennis, T., Beauchemin, V., Lavoie, N., 1993. Differential effects of olfactory bulbectomy on GABAA and GABAB receptors in the rat brain. Pharmacol. Biochem. Behav. 46, 77–82.

Drugan, R.C., Morrow, A.L., Weizman, R., Weizman, A., Deutsch, S.I., Crawley, J.N., Paul, S.M., 1989. Stress-induced behavioral depression in the rat is associated with a decrease in GABA receptor-mediated chloride ion flux and brain benzodiazepine receptor occupancy. Brain Res. 487, 45–51.

Duncko, R., Schwendt, M., Jezova, D., 2003. Altered glutamate receptor and corticoliberin gene expression in brain regions related to hedonic behavior in rats. Pharmacol. Biochem. Behav. 76, 9–16.

Fitzgerald, L.W., Ortiz, J., Hamedani, A.G., Nestler, E.J., 1996. Drugs of abuse and stress increase the expression of GluR1 and NMDAR1 glutamate receptor subunits in the rat ventral tegmental area: common adaptations among cross-sensitizing agents. J. Neurosci. 16, 274–282.

Fitzgerald, P.B., Oxley, T.J., Laird, A.R., Kulkarni, J., Egan, G.F., Daskalakis, Z.J., 2006. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res. 148, 33–45.

Fitzgerald, P.B., Sritharan, A., Daskalakis, Z.J., de Castella, A.R., Kulkarni, J., Egan, G., 2007. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. J. Clin. Psychopharmacol. 27, 488–492.

Frank, E., Salchner, P., Aldag, J.M., Salome, N., Singewald, N., Landgraf, R., Wigger, A., 2006. Genetic predisposition to anxiety-related behavior determines coping style, neuroendocrine responses, and neuronal activation during social defeat. Behav. Neurosci. 120, 60–71.

Frankowska, M., Filip, M., Przegalinski, E., 2007. Effects of GABAB receptor ligands in animal tests of depression and anxiety. Pharmacol. Rep. 59, 645–655.

Frenois, F., Moreau, M., O'Connor, J., Lawson, M., Micon, C., Lestage, J., Kelley, K.W., Dantzer, R., Castanon, N., 2007. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. Psychoneuroendocrinology 32, 516–531.

Gabbott, P.L., Warner, T.A., Jays, P.R., Salway, P., Busby, S.J., 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J. Comp. Neurol. 492, 145–177.

Gasparini, F., Spooren, W., 2007. Allosteric modulators for mGlu receptors. Curr. Neuropharmacol. 5, 187–194.

Gray, J., 1994. Framework for a taxonomy of psychiatric disorder. In: van Goozen, S., van de Poll, N.E., Sergeant, J. (Eds.), Emotions: Essays on Emotion Theory. Eribaum, Hillsdale, N.J., pp. 29–59.

Greenwood, B.N., Foley, T.E., Burhans, D., Maier, S.F., Fleshner, M., 2005. The consequences of uncontrollable stress are sensitive to duration of prior wheel running. Brain Res. 1033, 164–178.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 62, 429–437.

Grimm, S., Boesiger, P., Beck, J., Schuepbach, D., Bermpohl, F., Walter, M., Ernst, J., Hell, D., Boeker, H., Northoff, G., 2009a. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. Neuropsychopharmacology 34, 843–932.

Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Hell, D., Boeker, H., Northoff, G., 2009b. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical–cortical midline structures. Hum. Brain Mapp. 30, 2617–2627.

Gronli, J., Fiske, E., Murison, R., Bjorvatn, B., Sorensen, E., Ursin, R., Portas, C.M., 2007. Extracellular levels of serotonin and GABA in the hippocampus after chronic mild stress in rats. A microdialysis study in an animal model of depression. Behav. Brain Res. 181, 42–51.
Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacology 29, 1765–1781.
Hasler, G., van der Veen, J.W., Tumonis, T., Meyers, N., Shen, J., Drevets, W.C., 2007. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch. Gen. Psychiatry 64, 193–200.
Heidbreder, C.A., Groenewegen, H.J., 2003. The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. Neurosci. Biobehav. Rev. 27, 555–579.
Herman, J.P., Flak, J., Jankord, R., 2008. Chronic stress plasticity in the hypothalamic paraventricular nucleus. Prog. Brain Res. 170, 353–364.
Ho, Y., Liu, T., Tai, M., Wen, Z., Chow, R.S., Tsai, Y., Wong, C., 2001. Effects of olfactory bulbectomy on NMDA receptor density in the rat brain. Brain Res. 900, 214–218.
Hoover, W.B., Vertes, R.P., 2007. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct. Funct. 212, 149–179.
Huang, Y.H., Cheng, C.Y., Hong, C.J., Tsai, S.J., 2004. Expression of c-Fos-like immunoreactivity in the brain of mice with learned helplessness. Neurosci. Lett. 363, 280–283.
Jang, D.P., Lee, S.H., Park, C.W., Lee, S.Y., Kim, Y.B., Cho, Z.H., 2009. Effects of fluoxetine on the rat brain in the forced swimming test: a [F-18]FDG micro-PET imaging study. Neurosci. Lett. 451, 60–64.
Joels, M., Karst, H., Alfarez, D., Heine, V.M., Qin, Y., van Riel, E., Verkuyl, M., Lucassen, P.J., Krugers, H.J., 2004. Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. Stress 7, 221–231.
Kalueff, A.V., Nutt, D.J., 2007. Role of GABA in anxiety and depression. Depress Anxiety 24, 495–517.
Knorle, R., Assmann, D., Landwehrmeyer, G.B., Scheremet, R., Muller, K., Feuerstein, T.J., 1997. Aspartate, glutamate, glutamine, glycine and gamma-aminobutyric acid in human bioptic neocortical areas: comparison to autoptic tissue. Neurosci. Lett. 221, 169–172.
Kram, M.L., Kramer, G.L., Steciuk, M., Ronan, P.J., Petty, F., 2000. Effects of learned helplessness on brain GABA receptors. Neurosci. Res. 38, 193–198.
Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression. Nature 455, 894–902.
Kroes, R.A., Burgdorf, J., Otto, N.J., Panksepp, J., Moskal, J.R., 2007. Social defeat, a paradigm of depression in rats that elicits 22-kHz vocalizations, preferentially activates the cholinergic signaling pathway in the periaqueductal gray. Behav. Brain Res. 182, 290–300.
Laird, A.R., Fox, P.M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L., Turkeltaub, P.E., Kochunov, P., Fox, P.T., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum. Brain Mapp. 25, 155–164.
Li, C.X., Wang, Y., Gao, H., Pan, W.J., Xiang, Y., Huang, M., Lei, H., 2008. Cerebral metabolic changes in a depression-like rat model of chronic forced swimming studied by ex vivo high resolution 1H magnetic resonance spectroscopy. Neurochem. Res. 33, 2342–2349.
Lino-de-Oliveira, C., de Oliveira, R.M., Padua Carobrez, A., de Lima, T.C., del Bel, E.A., Guimaraes, F.S., 2006. Antidepressant treatment reduces Fos-like immunoreactivity induced by swim stress in different columns of the periaqueductal gray matter. Brain Res. Bull. 70, 414–421.
MacKenzie, E.M., Odontiadis, J., Le Melledo, J.M., Prior, T.I., Baker, G.B., 2007. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. Cell Mol. Neurobiol. 27, 541–574.
Maeng, S., Zarate Jr., C.A., 2007. The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. Curr. Psychiatry Rep. 9, 467–474.
Maeng, S., Zarate Jr., C.A., Du, J., Schloesser, R.J., McCammon, J., Chen, G., Manji, H.K., 2008. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol. Psychiatry 63, 349–352.
Matsuda, S., Peng, H., Yoshimura, H., Wen, T.C., Fukuda, T., Sakanaka, M., 1996. Persistent c-fos expression in the brains of mice with chronic social stress. Neurosci. Res. 26, 157–170.
Mayberg, H., 2002. Depression, II: localization of pathophysiology. Am. J. Psychiatry 159, 1979.
Mayberg, H.S., 2003. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging. Clin. N. Am. 13, 805–815.
McArthur, R., Borsini, F., 2006. Animal models of depression in drug discovery: a historical perspective. Pharmacol. Biochem. Behav. 84, 436–452.
Michael-Titus, A.T., Albert, M., Michael, G.J., Michaelis, T., Watanabe, T., Frahm, J., Pudovkina, O., van der Hart, M.G., Hesselink, M.B., Fuchs, E., Czeh, B., 2008. SONU20176289, a compound combining partial dopamine D(2) receptor agonism with specific serotonin reuptake inhibitor activity, affects neuroplasticity in an animal model for depression. Eur. J. Pharmacol. 598, 43–50.
Miczek, K.A., Nikulina, E., Kream, R.M., Carter, G., Espejo, E.F., 1999. Behavioral sensitization to cocaine after a brief social defeat stress: c-fos expression in the PAG. Psychopharmacology (Berl.) 141, 225–234.
Millan, M.J., 2009. Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs. Neurotherapeutics 6, 53–77.
Nemeroff, C.B., 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol. Psychiatry 1, 336–342.
Nikulina, E.M., Marchand, J.E., Kream, R.M., Miczek, K.A., 1998. Behavioral sensitization to cocaine after a brief social stress is accompanied by changes in fos expression in the murine brainstem. Brain Res. 810, 200–210.
Northoff, G., 2007. Psychopathology and pathophysiology of the self in depression—neuropsychiatric hypothesis. J. Affect. Disord. 104, 1–14.
Northoff, G., Bermpohl, F., 2004. Cortical midline structures and the self. Trends Cogn. Sci. 8, 102–107.
Northoff, G., Eckert, J., Fritze, J., 1997. Glutamatergic dysfunction in catatonia? Successful treatment of three acute akinetic catatonic patients with the NMDA antagonist amantadine. J. Neurol. Neurosurg. Psychiatry 62, 404–406.
Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain–a meta-analysis of imaging studies on the self. Neuroimage 31, 440–457.
Northoff, G., Panksepp, J., 2008. The trans-species concept of self and the subcortical–cortical midline system. Trends Cogn. Sci. 12, 259–264.
Northoff, G., Steinke, R., Czcervenka, C., Krause, R., Ulrich, S., Danos, P., Kropf, D., Otto, H., Bogerts, B., 1999. Decreased density of GABA-A receptors in the left sensorimotor cortex in akinetic catatonia: investigation of in vivo benzodiazepine receptor binding. J. Neurol. Neurosurg. Psychiatry 67, 445–450.
Northoff, G., Witzel, T., Richter, A., Gessner, M., Schlagenhauf, F., Fell, J., Baumgart, F., Kaulisch, T., Tempelmann, C., Heinzel, A., Kotter, R., Hagner, T., Bargel, B., Hinrichs, H., Bogerts, B., Scheich, H., Heinze, H.J., 2002. GABA-ergic modulation of prefrontal spatio-temporal activation pattern during emotional processing: a combined fMRI/MEG study with placebo and lorazepam. J. Cogn. Neurosci. 14, 348–370.
Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.
Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59.
Panksepp, J., 1998. Affectvie Neuroscience: The Foundations of Human and Animal Emotions. Oxford University Press, New York.
Panksepp, J., 2005. Affective consciousness: core emotional feelings in animals and humans. Conscious Cogn. 14, 30–80.
Persico, A.M., Schindler, C.W., Zaczek, R., Brannock, M.T., Uhl, G.R., 1995. Brain transcription factor gene expression, neurotransmitter levels, and novelty response behaviors: alterations during rat amphetamine withdrawal and following chronic injection stress. Synapse 19, 212–227.
Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol. Psychiatry 54, 515–528.
Pinna, G., Costa, E., Guidotti, A., 2006. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. Psychopharmacology (Berl.) 186, 362–372.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A. 98, 676–682.
Rakofsky, J.J., Holtzheimer, P.E., Nemeroff, C.B., 2009. Emerging targets for antidepressant therapies. Curr. Opin. Chem. Biol. 13, 291–302.
Ressler, K.J., Mayberg, H.S., 2007. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat. Neurosci. 10, 1116–1124.
Robbins, T.W., 1998. Homology in behavioural pharmacology: an approach to animal models of human cognition. Behav. Pharmacol. 9, 509–519.
Robichaud, M., Beauchemin, V., Lavoie, N., Dennis, T., Debonnel, G., 2001. Effects of bilateral olfactory bulbectomy on N-methyl-D-aspartate receptor function: autoradiographic and behavioral studies in the rat. Synapse 42, 95–103.
Salimi-Khorshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., Nichols, T.E., 2009. Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. Neuroimage 45, 810–823.
Salvadore, G., Cornwell, B.R., Colon-Rosario, V., Coppola, R., Grillon, C., Zarate Jr., C.A., Manji, H.K., 2009. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol. Psychiatry 65, 289–295.
Sanacora, G., Gueorguieva, R., Epperson, C.N., Wu, Y.T., Appel, M., Rothman, D.L., Krystal, J.H., Mason, G.F., 2004. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch. Gen. Psychiatry 61, 705–713.
Sartorius, A., Mahlstedt, M.M., Vollmayr, B., Henn, F.A., Ende, G., 2007. Elevated spectroscopic glutamate/gamma-amino butyric acid in rats bred for learned helplessness. Neuroreport 18, 1469–1473.
Seidel, K., Helmeke, C., Poeggel, G., Braun, K., 2008. Repeated neonatal separation stress alters the composition of neurochemically characterized interneuron subpopulations in the rodent dentate gyrus and basolateral amygdala. Dev. Neurobiol. 68, 1137–1152.
Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M.A., Wang, S., Coalson, R.S., Raichle, M.E., 2009. The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. U.S.A. 106, 1942–1947.
Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.F., Adriany, G., Hu, X., Ugurbil, K., 2002. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. Neuron 36, 1195–1210.

Shmuel, A., Augath, M., Oeltermann, A., Logothetis, N.K., 2006. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. Nat. Neurosci. 9, 569–577.
Shumake, J., Edwards, E., Gonzalez-Lima, F., 2003. Opposite metabolic changes in the habenula and ventral tegmental area of a genetic model of helpless behavior. Brain Res. 963, 274–281.
Shumake, J., Gonzalez-Lima, F., 2003. Brain systems underlying susceptibility to helplessness and depression. Behav. Cogn. Neurosci. Rev. 2, 198–221.
Skelin, I., Sato, H., Diksic, M., 2008. Olfactory bulbectomy reduces cerebral glucose utilization: 2-[14C]deoxyglucose autoradiographic study. Brain Res. Bull. 76, 485–492.
Skorzewska, A., Bidzinski, A., Hamed, A., Lehner, M., Turzynska, D., Sobolewska, A., Szyndler, J., Maciejak, P., Wisłowska-Stanek, A., Plaznik, A., 2009. The effect of CRF and alpha-helical CRF((9-41)) on rat fear responses and amino acids release in the central nucleus of the amygdala. Neuropharmacology 57, 148–156.
Stacey, A.E., Woodhall, G.L., Jones, R.S., 2002a. Activation of neurokinin-1 receptors promotes GABA release at synapses in the rat entorhinal cortex. Neuroscience 115, 575–586.
Stacey, A.E., Woodhall, G.L., Jones, R.S., 2002b. Neurokinin-receptor-mediated depolarization of cortical neurons elicits an increase in glutamate release at excitatory synapses. Eur. J. Neurosci. 16, 1896–1906.
Stone, E.A., Lehmann, M.L., Lin, Y., Quartermain, D., 2007. Reduced evoked fos expression in activity-related brain regions in animal models of behavioral depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 1196–1207.
Stone, E.A., Lin, Y., Quartermain, D., 2008. A final common pathway for depression? Progress toward a general conceptual framework. Neurosci. Biobehav. Rev. 32, 508–524.
Thakker-Varia, S., Alder, J., 2009. Neuropeptides in depression: role of VGF. Behav. Brain Res. 197, 262–278.
Thase, M.E., 2005. Bipolar depression: issues in diagnosis and treatment. Harv. Rev. Psychiatry 13, 257–271.
Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16, 765–780.
Ungless, M.A., Singh, V., Crowder, T.L., Yaka, R., Ron, D., Bonci, A., 2003. Corticotropin-releasing factor requires CRF binding protein to potentiate NMDA receptors via CRF receptor 2 in dopamine neurons. Neuron 39, 401–407.
Vertes, R.P., 2006. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. Neuroscience 142, 1–20.
Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.
Wager, T.D., Lindquist, M.A., Nichols, T.E., Kober, H., Van Snellenberg, J.X., 2009. Evaluating the consistency and specificity of neuroimaging data using meta-analysis. Neuroimage 45, S210–221.
Walter, M., Henning, A., Grimm, S., Schulte, R.F., Beck, J., Dydak, U., Schnepf, B., Boeker, H., Boesiger, P., Northoff, G., 2009. The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. Arch. Gen. Psychiatry 66, 478–486.
Webster, H.H., Flores, G., Marcotte, E.R., Cecyre, D., Quirion, R., Srivastava, L.K., 2000. Olfactory bulbectomy alters NMDA receptor levels in the rat prefrontal cortex. Synapse 37, 159–162.
Wieronska, J.M., Branski, P., Szewczyk, B., Palucha, A., Papp, M., Gruca, P., Moryl, E., Pilc, A., 2001. Changes in the expression of metabotropic glutamate receptor 5 (mGluR5) in the rat hippocampus in an animal model of depression. Pol. J. Pharmacol. 53, 659–662.
Zarate Jr., C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry 63, 856–864.