



Review

The 'resting-state hypothesis' of major depressive disorder—A translational subcortical–cortical framework for a system disorder

Georg Northhoff^{a,*}, Christine Wiebking^b, Todd Feinberg^c, Jaak Panksepp^d

^a University of Ottawa Institute of Mental Health Research, University of Hangzhou, China

^b Dept of Psychiatry, University of Magdeburg, Germany

^c Albert Einstein Medical College, New York, USA

^d State University of Washington, OK, USA

ARTICLE INFO

Article history:

Received 29 July 2010

Accepted 14 December 2010

Keywords:

Resting-state

Major depressive disorder

ABSTRACT

Major depressive disorder (MDD) has traditionally been characterized by various psychological symptoms, involvement of diverse functional systems (e.g., somatic, affect, cognition, reward, etc.), and with progress in neuroscience, an increasing number of brain regions. This has led to the general assumption that MDD is a stress-responsive brain 'system disorder' where either one or several alterations infiltrate a large number of functional systems in the brain that control the organism's somatic, affective, and cognitive life. However, while the effects or consequences of the abnormal changes in the functional systems of, for instance affect, cognition or reward have been investigated extensively, the underlying core mechanism(s) underlying MDD remain unknown. Hypotheses are proliferating rapidly, though. Based on recent findings, we will entertain an abnormality in the resting-state activity in MDD to be a core feature. Based on both animal and human data, we hypothesize that abnormal resting-state activity levels may impact stimulus-induced neural activity in medially situated core systems for self-representation as well as external stimulus (especially stress, specifically separation distress) interactions. Moreover, due to nested hierarchy between subcortical and cortical regions, we assume 'highjacking' of higher cortical affective and cognitive functions by lower subcortical primary-process emotional systems. This may account for the predominance of negative affect in somatic and cognitive functional system operations with the consecutive generation of the diverse symptoms in MDD. We will here focus on the neuroanatomical and biochemical basis of resting-state abnormalities in MDD including their linkage to the diverse psychopathological symptoms in depression. However, our 'resting-state hypothesis' may go well beyond that by being sufficiently precise to be linked to genetic, social, immunological, and endocrine dimensions and hypotheses as well as to clinical dimensions like endophenotypes and various diagnostic-prognostic biomarkers. Taken together, our 'resting-state hypothesis' may be considered a first tentative framework for MDD that integrates translational data, the various dimensions, and subcortical–cortical systems while at the same time providing the link to the clinical level of symptoms, endophenotypes and biomarkers.

© 2011 Elsevier Ltd. All rights reserved.

Contents

1. Introduction.....	1930
2. Neuroanatomy of the resting-state in depression.....	1931
2.1. Neuroanatomy Ia: radial-concentric organisation and subcortical–cortical systems in the healthy brain.....	1931
2.2. Neuroanatomy Ib: hierarchical and functional organisation in the healthy brain.....	1932
2.3. Neuroanatomy II: abnormal resting-state activity in the depressed brain.....	1934
3. Psychopathology of the resting-state in depression.....	1935
3.1. Psychopathology I: affective symptoms and reduced rest–stimulus interaction.....	1936
3.2. Psychopathology II: cognitive symptoms and (Ab)normal reciprocal modulation.....	1937
3.3. Psychopathology III: bodily symptoms and imbalance between intero- and exteroceptive stimulus processing.....	1937
3.4. Psychopathology IV: hopelessness and increased self-focus.....	1938

* Corresponding author at: Research Unit Director, Mind, Brain Imaging and Neuroethics, Depression Research Centre (DRC), Institute of Mental Health Research (IMHR), Room 6959, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada. Tel.: +1 613 7226521x6801.

E-mail address: georg.northhoff@rohcg.on.ca (G. Northhoff).

4.	Biochemistry of the resting-state in depression.....	1939
4.1.	Biochemistry I: biochemical modulation of rest–stimulus interaction in healthy subjects.....	1939
4.2.	Biochemistry II: biochemical modulation of rest–stimulus interaction in depressed subjects.....	1939
4.3.	Biochemistry III: a unified subcortical–cortical biochemical resting-state hypothesis.....	1940
5.	“Resting-state hypothesis” as unifying hypothesis for MDD.....	1941
5.1.	Resting-state hypothesis I: unification of different levels.....	1941
5.2.	Resting-state hypothesis II: endophenotypes and biomarkers.....	1942
6.	Conclusion.....	1942
	Acknowledgments.....	1943
	References.....	1943

1. Introduction

Major depressive disorder (MDD) is a complex psychiatric disorder that can be characterized by heterogeneity along several psychobiological dimensions. There is heterogeneity of symptoms in that MDD shows multiple psychopathological symptoms like anhedonia, social withdrawal, ruminations, psychomotor retardation, inner agitation, loss of motivation, increased self-focus, and diffuse bodily symptoms (Thase, 2005). To make matters even more complex, there is also a heterogeneity of affects in MDD with anxiety, sadness, grief, panic, and pain (Watt and Panksepp, 2009). Such heterogeneity of symptoms goes along with a heterogeneity of systems presumed to be involved in MDD; these include the endocrine, the affective, the immune, the autonomic-vegetative, and the cognitive systems (Price and Drevets, 2010; Watt and Panksepp, 2009). Neuroanatomically, there is also a heterogeneity of regions that are observed to be abnormal in MDD including both various cortical and subcortical regions with findings in humans showing predominantly cortical changes while animal models point out subcortical alterations (see Alcaro et al., 2010; Mayberg, 2009). The heterogeneity of regions is mirrored in the heterogeneity of biochemistry that, though focusing often on serotonin, also implicates other transmitters like GABA, glutamate, dopamine, adrenalin/noradrenaline, and acetylcholine (Drevets et al., 2008a,b; Savitz and Drevets, 2009a,b) and diverse neuropeptides, with current thinking favoring stress and reward-loss related dynorphin and corticotrophin releasing factor imbalances (see Panksepp and Watt, in press for recent overviews; Watt and Panksepp, 2009).

How does it all fit together, the different symptoms, the different systems, the various cortical and subcortical regions, and the different biochemical modulators? Recent hypotheses of MDD have focused on the limbic system including predominantly limbic-system related ventral and medial regions in forebrain and cortex (Alcaro et al., 2010; Drevets et al., 2008a; Mayberg, 2002, 2003, 2009; Philips et al., 2003; Price and Drevets, 2010; Savitz and Drevets, 2009a; Stone et al., 2003). Abnormal hyperactivity in limbic forebrain regions like the perigenual anterior cingulate cortex (PACC) is considered to be crucial in dysregulating the whole limbic and ventral visceral-emotional networks, down to the periaqueductal grey (PAG), with subsequent dysregulation of the lateral more dorsal somatic-cognitive networks on the cortical level including working-memory and thought related functions of the dorsolateral prefrontal cortex (DLPFC). What remains unclear though is how these cortical abnormalities as mostly observed in humans are related to the subcortical changes that are often reported in animal models of depression (see Alcaro et al., 2010). The question for subcortical–cortical integration is even more incomplete given the fact that they are closely integrated both anatomically and physiologically (see below for details). Psychopathologically, such imbalanced subcortical–cortical integration may engender excessive and persistent negative affect, most likely generated subcortically but percolating through higher cortical affective and cognitive functions.

While this predominantly limbic model of MDD accounts for many of the symptoms, it falls short of explaining the heterogeneity of systems, regions and biochemistries. Without an overarching and unifying psycho-pathophysiological framework to account for the heterogeneity of symptoms, systems, regions and biochemistry in MDD, a coherent understanding of MDD probably will not emerge. This heterogeneity of contributory variables has recently led to the assumption that MDD may be a ‘system disorder’ where the underlying disorder penetrates, permeates and infiltrates various functional systems in the brain both high (see Mayberg, 2009) and low (Harro and Oreland, 2001) within the neuroaxis. Lets compare the scenario in MDD to a viral infection. The effects or consequences of the virus, the various symptoms and their respective (neuronal) changes, are increasingly understood these days. It is even partly known how the virus itself penetrates into various functional systems accounting for the heterogeneity of symptoms. What remains unclear though is the virus itself, not only the type and species of virus, but even more basic, whether a viral type metaphor is appropriate at all. This means that we lack an adequate understanding of what causes and predisposes the kind of neuronal changes we observe during the various symptoms in MDD.

Many are considering disruptions in brain growth factors and imbalanced transcription factors and perhaps long-term epigenetic histone acetylation changes that control the expressions of multiple genes (see Watt and Panksepp, 2009 for review). Others have proposed inflammation, based on abundant convergent evidence, while some cultivate the role of cytokines and interleukins that are intermediate immune system modulators and there are increasing numbers of hypotheses that focus on dietary and other environmental stress factors (Anisman, 2009). Much of this work is conducted under the general diathesis-stress model (McEwen, 2007). Surprisingly, perhaps the least cultivated furrow of thought in the neurosciences is with regard to specific emotional-affective reward and punishment network functions of the brain (Nestler and Carlezon, 2006; Watt and Panksepp, 2009). With this much diversity, one can be confident that MDD is a multi-factorial disorder, and that it comes to be manifested in various distinct forms, with varying intensities and patterns of penetrance. Obviously, to make empirical progress one has to be selective, which may often lead to an excess focus on the many parts as opposed to the global wholes – the massive psychological state-shifts of depressions. Here we will focus on an emerging global views that generates new neuroscientific and clinical predictions.

One of the most consistent findings among the variety of different and in part contradictory findings in MDD is the observation of abnormalities in resting medial brain-state activity. Human imaging studies, using both PET and FMRI, have reported abnormally elevated resting-state activity (activity in the absence of any specific external stimulation), in ventral anterior medial cortical regions like the PACC, the subgenual anterior cingulate cortex (SUACC), and the ventromedial prefrontal cortex (VMPFC) (Alcaro et al., 2010; Fitzgerald et al., 2006; Greicius et al., 2007; Grimm

et al., 2009a; Mayberg, 2002, 2003; Sheline et al., 2009). These medially situated, higher affective–limbic regions of brain are intimately related to various basic subcortical emotional systems that mediate primary-process emotionality (Panksepp, 1998). In contrast to these medial regions, lateral regions like the DLPFC, which mediates more purely cognitive functions, often exhibit hypoactivity during recording of the resting-state in MDD patients (see Alcaro et al., 2010; Fitzgerald et al., 2006). This highlights a general pattern of brain activity. The medial and lateral cortical forebrain regions are typically in sea-saw balance (Northoff et al., 2004) when medial interoceptive and emotional systems are aroused, then more cognitive (external information-processing) DLPFC systems are inhibited, which tilts the other way when lateral cognitive mechanisms become engaged (Liotti and Panksepp, 2004).

Also, animal models of MDD have observed increased resting-state activity in the forebrain including the ACC and in various subcortical limbic regions including the raphe nucleus, the locus coeruleus, the septum, and the PAG (see Alcaro et al., 2010 for an overview; see also Krishnan and Nestler, 2008; Mällo et al., 2009; Ressler and Mayberg, 2007; Shumake et al., 2003). Biochemically, resting-state hyperactivity in the human PACC has recently been directly associated with GABA and glutamate (see Sanacora, 2010; Walter et al., 2009) while subcortical resting-state hyperactivity seems to be modulated prominently by deficits in GABA-A receptors and hyperfunction of NMDA-A receptors (Alcaro et al., 2010), which is not to say that many other neurochemical systems are not involved. Taken together, these data indicate the linkage of resting-state hyperactivity with specific brain regions, biochemical vectors and thereby mental functions.

The aim of this paper is to develop these findings of abnormalities in the resting-state into a testable hypothesis about the pathophysiology of MDD, the ‘resting-state hypothesis’ as we call it. The core features of our resting-state hypothesis are the following: (i) the integration of human and animal data thus being translational; (ii) the integration of subcortical and cortical changes assuming a coherent subcortical-cortical unity; (iii) the integration of the different functional systems of interoception, affect, cognition, reward, etc.; (iv) the integration of the different dimensions ranging from the molecular-genetic over the neuroanatomical and biochemical to the psychopathological and clinical levels. In short, our ‘resting-state hypothesis’ aims to account for MDD as a specific brain system-network disorder.

We assume that such multi-dimensional hypotheses can help bridge the many evident gaps in existing theories; this hypothesis takes us from the level of brain regions to the level of specific brain networks and psychological symptoms, while at the same time providing abundant ways to link to diverse biochemical and genetic-molecular mechanisms. In other words, we will argue that the ‘resting-state hypothesis’ may provide a unifying and overarching framework that can bridge the gap between the different levels of the nervous systems. This in turn makes it possible to account for the above-mentioned heterogeneity of symptoms, systems, regions, and biochemistries in MDD, while remaining intimately conversant with the various translational neurobiological findings. This hypothesis has the potential to refine the search for relevant endophenotypes and biomarkers (Hasler et al., 2004; Panksepp, 2006), an issue we will turn to at the very end of our paper.

2. Neuroanatomy of the resting-state in depression

The first part of this resting-state hypothesis in depression focuses on the neuroanatomy of abnormal resting-state activity. In order to understand the abnormal pattern of resting-state activity across different regions, we need to go back to the neuroanatomy and functional and hierarchical organisation of the healthy brain.

2.1. Neuroanatomy Ia: radial-concentric organisation and subcortical–cortical systems in the healthy brain

The hierarchical organization of the brain, the only organ that has a semi ‘stratified’ evolutionary organization can, in the most straightforward way, be seen as set of concentric rings, as originally encapsulated by Paul MacLean’s triune brain concept (MacLean, 1990). Within these layers, we can see a diversity of (i) primary-process brain–mind mechanisms that serve bodily integrity, partly through various basic emotional-affective systems that encode biological values that are built into the system (i.e., they mediate ‘instincts’ that are truly ancestral memories), surrounded by (ii) various basic classical-conditioning and instrumental learning mechanisms, that allow basic values to be connected to world events, all of which is surrounded by and interconnected with (iii) cortical mechanisms that allow for very complex forms of affective state and cognitive information processing that can promote higher brain functions ranging from obsessive ruminations about psychologically ‘painful’ feelings to logical-propositional thoughts about the world.

Let us express this vision in more concrete anatomical terms: Nieuwenhuys (1996); Nieuwenhuys et al. (1988, 2007) assumed a medio-lateral trend in subcortical regions that are located concentrically or radially around the ventricle, e.g., the aqueduct, with progressive extension from median to lateral locations. Based on various distinct features (see below), he distinguished the subcortical regions into three distinct territories, core, median and lateral paracore, and lateral regions which, despite being closely interconnected, can be distinguished from each other. Core subcortical regions refer to those regions that are located in direct proximity to the ventricle and may thus be described as paraventricular or periaqueductal; these regions include the PAG, the pontine central gray, the medial hypothalamus, the septum, the parabrachial nuclei and the dorsal vagal complex. While the subcortical median paracore regions are located directly adjacent to the core regions; subcortical median paracore regions include the series of raphe nuclei, the lateral hypothalamus, the bed nucleus of the stria terminalis. These are closely connected to the bilateral paracore regions that include the ventral tegmental area (VTA), the locus coeruleus, the substantia nigra, the nucleus reticularis.

The two inner rings (core and median and lateral paracore regions), can be distinguished from the most outer ring, the lateral regions, with respective to their fibres (myelinated or unmyelinated), biogenic amines (serotonin, noradrenaline/adrenaline, dopamine, histamine), circumventricular organs, gonado-steroid receptors, and coherent behavior (e.g., as induced by localized electrical stimulation of the brain) (see Nieuwenhuys, 1996, pp. 560–7; and Panksepp, 1998 for details). This can lead us to consider core and median and lateral paracore regions (see Fig. 1a) together as unity which functionally can be characterized by their predominant involvement in processing interoceptive stimuli thereby regulating the body’s homeostatic milieu, vegetative-autonomic functions, and a variety of specific emotional and motivational processes. Especially the core regions, the inner ring, is strongly implicated in homeostatic and basic emotional regulations. This distinguishes them from the most lateral regions on the subcortical level like the crus and the colliculi that, by sending integrated inputs to the spinal cord, are implicated in processing exteroceptive and sensorimotor stimuli.

Based on MacLean’s and Nauta’s concept of the limbic system, Nieuwenhuys (1996); Nieuwenhuys et al. (2007) proposes extension of the core–paracore system into the forebrain. Mesencephalic core–paracore regions are closely connected to the hypothalamus and various regions in the forebrain including the amygdala, septum, the hippocampus, and parahippocampal gyrus. This led to the concept of the ‘greater, distributed or extended limbic sys-

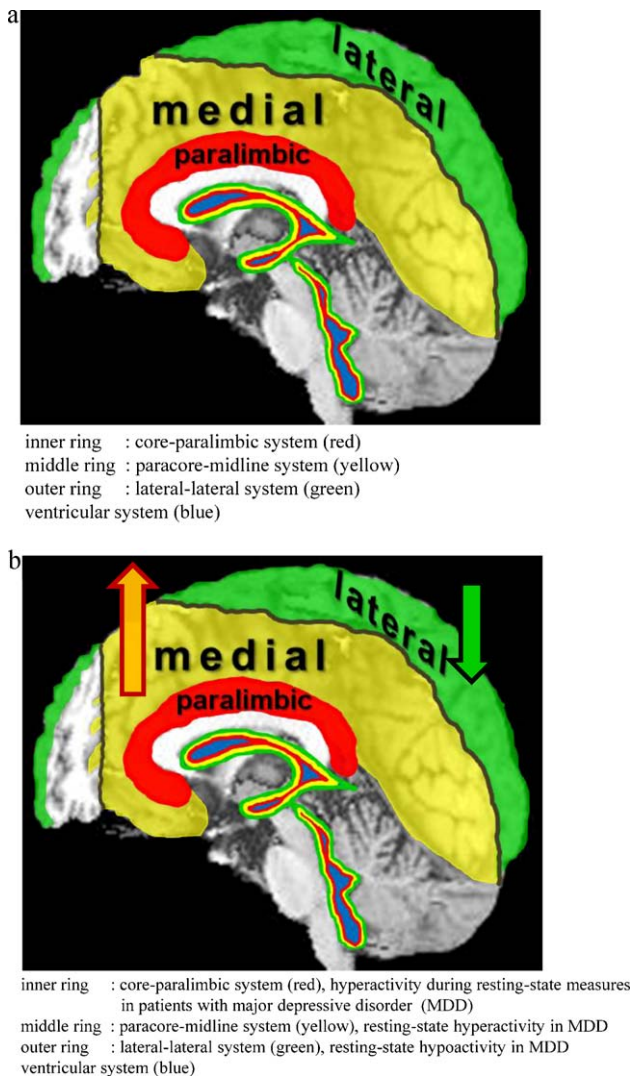


Fig. 1. (a) Radial-concentric organisation and subcortical-cortical systems in the healthy brain.

tem' (de Olmos and Heimer, 1999; Heimer, 2003; Morgane et al., 2005; Morgane and Mokler, 2006). This was even further developed by Mesulam (2000) who extended the originally mesencephalic core regions over the forebrain (the limbic system, into the cortex itself, namely 'paralimbic areas'). Paralimbic areas are those regions in the cortex that are anatomically linked to ancient emotional and motivational networks, located right around and thus adjacent to the ventricle, so those heavily paleocortical regions can be regarded as extensions of the originally mesencephalic grouping of the core regions. These paralimbic areas include the lower parts of the orbitofrontal cortex, the perigenual, supragenual anterior cingulate cortex (PACC, SACC), the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC), the temporal pole and the insula.

Taking the radial-concentric organisation into rings on the subcortical mesencephalic level and its extensions into the forebrain as the starting point, Feinberg (2009) argues that the three postulated rings are also manifest and visible on the level of the cortex. The outer or the most peripheral ring as being the furthest away from the ventricle includes regions like the sensory cortex, the motor cortex, and the lateral prefrontal, parietal and occipital regions. These regions may be considered as the cortical extension of the most lateral regions on the subcortical level, e.g., the mesencephalic crus and colliculi. Analogous to the lateral regions on the subcortical regions, the lateral cortical regions, the outer

ring, are involved predominantly in processing external stimuli as distinguished from the interoceptive stimulus processing of the inner most ring. This provides an anatomical distinction between exogenously driven cognitive processes and endogenously driven primary-process homeostatic, motivational and core emotional processes (Panksepp, 1998).

Feinberg (2009) also assumes a middle ring on the cortical level that is located in-between inner and outer rings and thus between paralimbic and lateral cortical regions. This middle ring on the cortical level includes regions like the medial orbitofrontal cortex, the ventromedial and dorsomedial prefrontal cortex (VMPFC, DMPFC) and the medial parietal cortex (MPC) which have recently been subsumed under the concept of cortical midline structures (CMS) (Northhoff and Bermppohl, 2004; Northhoff et al., 2006). Since it is sandwiched in-between inner and outer rings and their involvement in intero- and exteroceptive processing respectively, Feinberg (2009) assumes this middle ring to account for integrating and linking both kinds of stimuli, i.e., intero-exteroceptive integration¹. The CMS do grossly overlap with what especially in the imaging domain is often described as the default-mode network (DMN) that is supposed to be characterized by particularly high resting-state activity, e.g., intrinsic activity (see above in chapter 1 of this part as well as Buckner et al., 2008; Raichle et al., 2001). How such high intrinsic or resting-state activity in the CMS is related to intero-exteroceptive integration, as postulated by Feinberg (2009) remains unclear, though.

Lets summarize this subcortical-cortical system that is based on various anatomical (e.g., cytoarchitectonic, chemoarchitectonic), and connectional features (see Fig. 1a). The subcortical core regions adjacent to the aqueduct extend over the forebrain and the limbic regions into the cortex where they surface as paralimbic regions. One may consequently want to speak of a 'core-paralimbic system'. The next concentric ring are the median and lateral paracore regions on the subcortical level that extend over the forebrain and its limbic system into the midline regions on the cortical level; one may consequently want to speak of a 'paracore-midline system'. Finally, the very lateral subcortical regions, where sensory and motor fibres connect it to the spinal cord, extend cortically into lateral cortical regions as the most outer or peripheral ring, which can be envisioned as a 'lateral-lateral system' in the following. Such lateral subcortical extensions onto lateral cortical level suggest that the information-processing of those subcortical perceptual regions are refined on the cortical level. In other words, vague perceptions are converted into highly focussed, precise perceptions.

2.2. Neuroanatomy Ib: hierarchical and functional organisation in the healthy brain

Carhart-Harris and Friston (2010) and Friston (2010) suggest an anatomical and hierarchical organisation of the brain that is different from the radial-concentric organisation of subcortical-cortical systems as suggested here. Rather than taking anatomical features

¹ What though remains unclear whether such intero-exteroceptive integration on the cortical level corresponds to analogous processes on the level of the forebrain and the mesencephalon. One could for instance imagine that what is described as core system on mesencephalic level may extend into the paralimbic areas since both are located directly adjacent to the aqueduct/ventricle. While the median and lateral paracore regions on the mesencephalic level may correspond to the middle ring on the cortical level and thus cortical midline structures. Support comes here from the connectivity pattern. Cortical regions like the anterior cingulate (PACC, SACC, PCC), the caudal orbitofrontal cortex, the temporal poles and the insula are characterized by strong inputs from especially the subcortical core regions like the PAG (see Nieuwenhuys, 1996, 573). In contrast, the VMPFC and the DMPFC receive for instance strong input from especially the raphe nuclei as median paracore regions and the locus coeruleus as lateral paracore region (see Morgane et al., 2005; Nieuwenhuys, 1996).

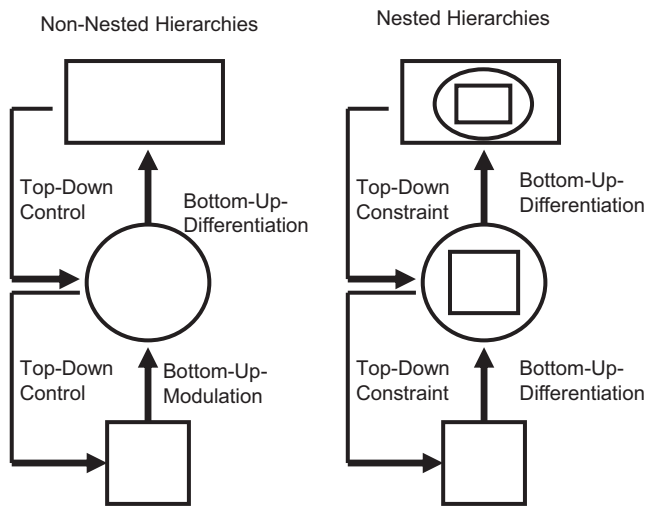


Fig. 2. Different forms of hierarchies.

as roadmap, as in the case of the subcortical–cortical systems, they take psychological and more specifically cognitive features as their guiding vision. They suggest that the thalamic nuclei, the unimodal sensory regions, and the other subcortical limbic and paralimbic regions are the lowest level in a functional hierarchy. The next higher levels promote psychological “salience” partly via the dorsal attention systems. The salience system includes the dorsal anterior cingulate cortex, the frontoinsula cortices, the amygdala, and the ventral midbrain. While the dorsal attention system concerns the dorsolateral prefrontal cortex, the frontal eye fields, the dorsal medial prefrontal cortex, the intraparietal sulcus, and the superior parietal lobule (see Carhart-Harris and Friston, 2010 p. 6, for details and references). Finally, the third and top level is to be found in what is called the default-mode network (DMN), concentrated in medial-rostral regions of the brain, that shows high activity in the brain’s resting-state and predominant deactivation during stimulus-induced activity.

These three levels, the DMN at the top, the attentional systems at intermediate levels, and the sensory/limbic/paralimbic regions at the lowest, are postulated to form a functional hierarchy. Each level has its own neurodynamics, which regulate the dynamics of the other levels. Spontaneous activity (oscillations and fluctuations), in for instance the DMN suppress and regulate spontaneous activity in the attention systems as well as limbic and paralimbic regions via top-down modulation. While spontaneous activity in the attention networks controls and inhibits neural activity changes induced by exogenous sensory input in thalamic and sensory cortical regions (see Carhart-Harris and Friston, 2010, pp. 11–12, for details).

Since the subordinate systems are suppressed and controlled by the next higher one, one may speak here of top-down control while the lower regions’ activity itself is only there to be controlled and suppressed. Carhart-Harris and Friston (2010) argue that the top-down control of the highest level, the DMN, over the subsequent lower levels of the hierarchy, restricts the neurodynamics associated with the latter (see Fig. 2a). Such a model of ‘top down control’ makes two crucial presuppositions: (i) clear-cut anatomo-functional segregation between higher and lower levels and regions; (ii) Inhibition and suppression as main functions of top-down control of higher onto lower levels of the hierarchy. We present such alternatives to highlight that there are several ways to envision hierarchical regulations, and each cannot be of equal validity. Options need to be winnowed empirically.

While many studies affirm inhibitory and suppressive influences of the medial prefrontal cortex on the amygdala, the exact

impact of other regions of the DMN like the posterior cingulate cortex (PCC) and the perigenual anterior cingulate cortex (PACC) on subcortical regions remain far from clear. Also there is some evidence that the impact of the DMN regions on others may not only be suppressive but also facilitating and enabling, which better fits the concept of “regulation” rather than just inhibitory control. This is most apparent in the above mentioned findings concerning rest–stimulus interaction where regions of the DMN may enable and predispose stimulus-induced activity in, for instance, sensory and limbic/paralimbic regions (see Northhoff et al., 2010 for review). Hence to assume simple suppression and inhibition would be to neglect the facilitating and thus enabling and predisposing neural effects of the brain’s high resting-state activity in the DMN on the neural activity of other regions during stimulus-induced activity. This sheds some doubt on whether the hierarchical model of top-down control, with suppression and inhibition as its essential ingredients, is empirically plausible as overall model of brain organisation. Clearly, as knowledge advances, we are bound to require more and more subtle regulatory views in order to make sense of the data.

Instead of clear-cut segregation, there is mutual integration and dependence between the different systems resulting in what Feinberg (2009, pp. 167) describes, in line with abundant evolutionary thought (MacLean, 1990; Panksepp, 1998) as “nested hierarchies” (see Fig. 2b), where levels of control are in mutual dynamic interaction. Unlike in non-nested hierarchies where there is indeed clear-cut segregation between higher and lower levels, with the former exerting top-down control over the latter; thus, unidirectional top-down and bottom-up distinctions between higher and lower controls remains impossible in nested hierarchies. Nested hierarchies are characterized by the combination of lower brain functions being re-represented within higher brain functions, with the former resurfacing, as function of learning, within the latter; what is described as bottom-up modulation and top-down control in non-nested hierarchies reappears as constraint of the whole system and its organisation and structure (see Feinberg, 2009, pp. 167).

In other words, the evolutionary layers of brain function are in dynamic two way control with dynamic “circular” interactions being the rule rather than the exception. With such two-way up-down and medial–lateral causal systems, one needs to specify the conditions under which certain flows of control prevail, and those where the reverse is true, all the while understanding that only some of the deviations from homeostasis tend to yield psychiatrically significant symptoms. For instance, in depression, bottom-up controls may prevail, indicating why top-down cognitive-behavioral therapies are so effective. However, this does not mean that laterally propagating controls where one primary-process system for affect, such as joyful playfulness, can counteract overactive negative systems such as feelings of separation distress.

Thus, such nested hierarchies can be observed not only at the anatomical levels of the brain but also in terms of overall functional integrations. For instance, a recent study on mind-wandering during external stimulation (a working memory task), observed neural activity in both DMN and cortical attention system levels (Christoff et al., 2009). And deactivations (negative BOLD responses) were observed in both the DMN as well as primary sensory and motor cortices, and caudally at least to the ventral striatum (de Greck et al., 2008). Taken together, these results shed some doubt on the supposition of clear-cut anatomo-functional segregation between DMN and attention systems (and limbic–subcortical regions). With no clear-cut segregation as should have been predicted, the assumption of clear directional top-down control of the one by the other seems doubtful.

Another empirical presupposition of the Carhart-Harris and Friston (2010) view is that unidirectional top-down control is sustained by unilateral inhibitory and suppressive impact of higher

brain regions on lower ones. While there are many studies showing inhibitory and suppressive influences of the medial prefrontal cortex on the amygdala, as cited by the authors, the exact impact of other regions of the DMN like the posterior cingulate cortex (PCC) and the perigenual anterior cingulate cortex (PACC) on subcortical regions remain far less clear. Also there is some evidence that the impact of DMN regions on others may not only be suppressive but also facilitating and enabling. This is most apparent in the above mentioned results on rest–stimulus interaction where regions of the DMN may enable and predispose stimulus-induced activity in for instance sensory and limbic/paralimbic regions. Hence to assume simple suppression and inhibition would be to neglect the facilitating and thus enabling and predisposing neural effects of the brain's high resting-state activity in the DMN on the neural activity of other regions during stimulus-induced activity. Overall, this sheds doubt on whether the hierarchical model of top-down control operating mostly with suppression and inhibition² is a plausible overall model of brain organisation. At this point, it is wiser to envision two-way, circular, causality, whereby under some conditions top-down processing tends to prevail in both excitatory as well as more empirically established inhibitory ways, but that under other conditions, perhaps in depression, the bottom-up emotional facilitation of sustained cognitive ruminations takes over. This coaxes investigators to specify the conditions that lead to global shifts in such regulatory dynamics of the nested cognition-affective interactions.

Taken together, the widely presumed cognitively-guided anatomical and hierarchical organisation of global “top-down controls” remains empirically implausible considering both the brain's anatomical and functional features. Instead of clear-cut segregation, the clear alternative is that there is mutual integration and dependence between the different systems resulting in what Feinberg (2009, 167ff), among others, envisions as a “nested hierarchy” (see Fig. 2). Non-nested hierarchies presuppose more clear-cut segregation, yielding more discrete higher and lower levels, with the former exerting top-down control over the latter. Nested hierarchies, in contrast, are characterized by interactions between the lower and higher level regions, with lower level functions often ‘resurfacing’ within the context of higher order functions; what is described as bottom-up modulation and top-down control in non-nested hierarchies reappears as constraint of the whole system and its organisation and structure (see Feinberg, 2009, pp. 167).

The model of “nested hierarchy” provides a realistic, empirically plausible description of subcortical-cortical interactions. The lower subcortical levels of control are extended and re-appear contextualized in cognitive features added by higher limbic and cortical levels. While the model of “nested hierarchy” nicely accounts for the general functional interactions widely thought to control subcortical-cortical integrations (see Feinberg, 2009 for details), the exact functional implications for the neuropsychological processing of such interactions remain to be well studied. We would suggest that functionally nested hierarchies no longer entail “top-down control” as a hallmark, as is the case with non-nested hierarchies, but rather by more subtle blends that might be described as ‘bottom-up differentiation’ and ‘top-down constraint’.

By continuously realizing or better nesting the lower systems (the subcortical ones) within higher systems (the higher limbic

and cortical ones), the whole integrated complex continues to be differentiated in bottom-up ways. Such bottom-up differentiation may for instance be of critical importance for understanding how ancient primary-process subcortical emotional systems (e.g., Panksepp, 1998) contribute to broad-scale psychiatric disorders such as MDD. In this view, the raw psychological pain of social loss (arousal of the separation-distress mediating GRIEF/PANIC system may set the stage for painful memories and ruminations (Watt and Panksepp, 2009). In other words, such bottom-up differentiation may be regarded as the continuation of the neural processing of the lower affective systems, recontextualized in more sophisticated cognitive ways. Thereby, incoming stimuli are continuously re-processed through higher regions and thereby become increasingly differentiated. The converse is possible too. In this case, the ‘higher’ regions exert some regulatory modulation (rather than just inhibitory control) on the ‘lower’ regions so that one may want to speak of ‘top-down constraint’. Accordingly, *bottom-up differentiation* and *top-down constraint*, with ‘circular two-way-causation’ replace, in nested hierarchies, what has traditionally been described as top-down control and bottom-up modulation in non-nested hierarchies³.

2.3. Neuroanatomy II: abnormal resting-state activity in the depressed brain

Because of several excellent reviews about the structural and functional brain changes in MDD (Alcaro et al., 2010; Mayberg, 2002, 2003, 2009; Philips et al., 2003; Price and Drevets, 2010), we here briefly highlight only the main findings and conclusions from these various reviews and then relate them to functional networks as delineated in normal-healthy brains.

Alcaro et al. (2010) conducted a meta-analysis of all imaging studies in human MDD that had focussed on resting-state activity. This yielded hyperactive regions in the PACC, the VMPFC, thalamic regions like the dorsomedial thalamus and the pulvinar, pallidum/putamen and midbrain regions like the VTA, Substantia nigra (SN), the Tectum and the PAG. In contrast, resting-state activity was hypoactive and thus reduced in the dorsolateral prefrontal cortex (DLPFC), the posterior cingulate cortex (PCC) and adjacent precuneus/cuneus (Alcaro et al., 2010). These results are well in accord with other meta-analyses (see Fitzgerald et al., 2006, 2008; Price and Drevets, 2010; Savitz and Drevets, 2009a). Also, Price and Drevets (2010) and Savitz and Drevets (2009a,b) emphasized the role of the hippocampus, parahippocampus and the amygdala where resting-state hyperactivity was also evident in MDD. Interestingly, the very same regions and the PACC also show structural abnormalities with reduced gray matter volume in imaging studies and reduced cell counts markers of cellular function in post-mortem studies (see Price and Drevets, 2010 and Savitz and Drevets, 2009a,b).

Involvement of these regions in MDD is further corroborated by the investigation of resting-state activity in animal models of MDD. Reviewing evidence for resting-state hyperactivity in various animal models, yielded diverse participating brain regions – the anterior cingulate cortex, the central and basolateral nuclei of the amygdala, the bed nucleus of the stria terminalis, the dorsal raphe, the habenula, the hippocampus, the hypothalamus, the nucleus accumbens, the PAG, the DMT, the nucleus of the solitary tract, and the piriform and prelimbic cortex (Alcaro et al., 2010). In contrast, evidence of hypoactive resting-state activity in animal models remains sparse with no clear results (Alcaro et al., 2010).

² Note that this is not to deny empirical evidence of suppression and inhibition; it is only to deny that inhibition and suppression entail a certain hierarchical organisation, e.g., top-down control, since that assumption does not seem to be supported clearly by current empirical data. I hence deny that there is empirical evidence of making the inference from the empirical data about inhibition and suppression and other empirical data concerning rest–stimulus interaction to the assumption of a specific hierarchical organisation as top-down control.

³ I am fully aware that the here suggested concept of nested hierarchies needs more detailed elaboration which though would be beyond this book (see Feinberg, 2009, chapter 6).

These findings indicate abnormally high resting-state activity in extended subcortical and cortical medial regions of the brain. This has let authors like Philips (Philips et al., 2003), Mayberg (Mayberg, 2002, 2003, 2009) and Drevets (see Price and Drevets, 2010; Savitz and Drevets, 2009a,b) to assume dysfunction in the limbic system in depression or more specifically in the 'limbic-cortico-striato-pallido-thalamic circuit' with reciprocal interactions between medial prefrontal and limbic regions being crucial (Price and Drevets, 2010). This now needs to be extended to include subcortical primary-process emotional regions on the mesencephalic level as suggested by the animal data. In addition, one human study has found con-current involvement of both cortical and subcortical regions in resting-state hyperactivity (Grimm et al., 2009a). Relying on pure perceptual rather than cognitive tasks, these investigators (indirectly through analysis of stimulus-induced activity/deactivation in resting-state regions) demonstrated concurrent resting-state hyperactivity within medial cortical structures (paralimbic and midline regions), as well as subcortical levels (e.g., PAG, thalamus, tectum).

How do these findings fit into the above delineated anatomical characterization of the healthy brain? What was conceptualized as inner and middle rings at the cortical level (*vide supra*), the paralimbic areas and the cortical midline structures, generally show hyperactivity during resting-state measures in MDD people (see Fig. 1b). These regions in the inner and middle rings were considered as cortical extensions of the core–paracore and limbic–forebrain regions. Interestingly, human and predominantly animal data show exactly these regions, the limbic forebrain regions like the amygdala, the hypothalamus, and the hippocampus as well as the mesencephalic core–paracore areas like the raphe nuclei, the locus coeruleus, the habenula, and the nucleus of the solitary tract to be hyperactive during resting-states. Hence, the more global picture may simply arise from the fact that the mesencephalic core–paracore system is extended anatomically and functionally into the forebrain – e.g., the limbic system, and associated cortical regions – the paralimbic areas and the cortical midline structures, which synergize with resting-state hyperactivity in the above mentioned subcortical and cortical regions in MDD.

Another observation fits well with this anatomical model in the healthy brain. The outer ring covers the lateral regions on the cortical level like the dorsolateral prefrontal cortex and the sensory and motor regions. Especially in the DLPFC and in part also in the motor cortex (see Alcaro et al., 2010), resting-state hypoactivity has been consistently observed, especially in people with MDD (see Fig. 1b). Another region showing reduction of activity is the visual cortex where the concentration of GABA has been found to be reduced (Maciag et al., 2010; Sanacora et al., 1999). Mirroring Mayberg's (2002, 2003, 2009) distinction between ventral and dorsal systems, these findings suggest resting-state activity imbalances between inner/middle and outer cortical rings and thus between paralimbic/midline and lateral cortical regions.

Considering these findings together, resting-state activity in MDD may be characterized by a subcortical–cortical imbalance between inner/middle and lateral rings. More specifically, the subcortical core–paracore regions seem to be hyperactive in the resting-state which is extended over the forebrain regions to the cortical level of paralimbic areas and cortical midline structures. In contrast, subcortical and especially cortical regions of the lateral-cognitive ring, like the lateral prefrontal cortex and the sensory-motor cortices, seem to show rather hypoactivity in the resting-state. From a purely anatomical perspective, one could envision this dysbalance gradually spreading between the inner-middle and outer rings in the radial-concentric organisation across subcortical and cortical regions.

3. Psychopathology of the resting-state in depression

So far we have considered the neuroanatomy of the resting-state in MDD with the findings suggesting dysbalance between hyperactive inner-middle and hypoactive outer subcortical–cortical rings. What do these abnormalities in the subcortical–cortical resting-state pattern imply for the psychopathology in MDD? How are different symptoms, like affective and cognitive symptoms, bodily symptoms, hopelessness and increased self-focus related to the dysbalance between the different subcortical and cortical systems?

The above described abnormal pattern of resting-state hyper- and hypoactivity in the respective subcortical–cortical systems may strongly impact the neural processing of external stimuli in these regions. The abnormal resting-state activity leads to reduced rest–stimulus interaction (see Northoff et al., 2010 for a recent review) in the functional impacted systems (e.g., affective, cognitive, reward, etc.), and their respectively associated subcortical–cortical regions, which in turn may enable and predispose the occurrence of the different symptoms in MDD. Hence, to better understand the pathophysiology of the various symptoms, we have to investigate rest–stimulus interaction in the different functional systems (see below for details).

The other question one may raise is how changes in the above described subcortical–cortical systems translate into complex depressive symptoms, especially considering the aforementioned functional and hierarchical organisations? First, let us re-emphasize evidence for a nested rather than non-nested hierarchy. Nested hierarchy can be characterized by bottom-up differentiation and top-down constraint rather than top-down control and bottom-up modulation. Changes in the balance between the subcortical–cortical systems may then also affect how the different functional systems associated with the former can interact with each other. For instance, the interactions between the more subcortical affective and more cortical cognitive systems as well as the various subcortical, reward and punishment – positive and negative affect functions – may be altered in depression.

Most importantly, in addition to the interaction between the different functional systems, the nested character of the functional and hierarchical organisation may be crucial in spreading the subcortical resting-state hyperactivity to the cortical level. And this subcortical hyperactivity may be heavily influenced in MDD by affectively negative primary-process emotional systems such as FEAR, RAGE and most especially the separation-distress PANIC/GRIEF systems (for full discussion, see Panksepp, 1998, 2005; Watt and Panksepp, 2009). Related functional systems on the cortical-cognitive level may thus be affectively modulated or high-jacked by diverse forms of unreflective negative affects through presently unidentified subcortical abnormalities, but according to studies of social-emotional processes, especially by excessive PANIC/GRIEF processes; this negative-affect may be consolidated and intensified further by gradual reduction of positive affect more directly through diminished reward-SEEKING urges (for full discussions of these options, see Panksepp and Watt, in press; Watt and Panksepp, 2009). Taken together, this may lead to widespread involvement of different functional systems and consecutively to the broad variety of different symptom spectrums in depression. In other words, the diffuse and variable psychopathological systems may be due to the widespread subcortical impact on the discussed widely ramifying nested-hierarchical networks along with various functional reorganization of subcortical–cortical systems. Due to such nested hierarchies, the abnormal subcortical resting-state activity may imprint itself abnormally strongly on cortical patterns of neural activity. One may even speak of subcortical high-jacking of limbic/paralimbic and medial and lateral cortical regions by abnormal subcortical resting-state activity and the respectively

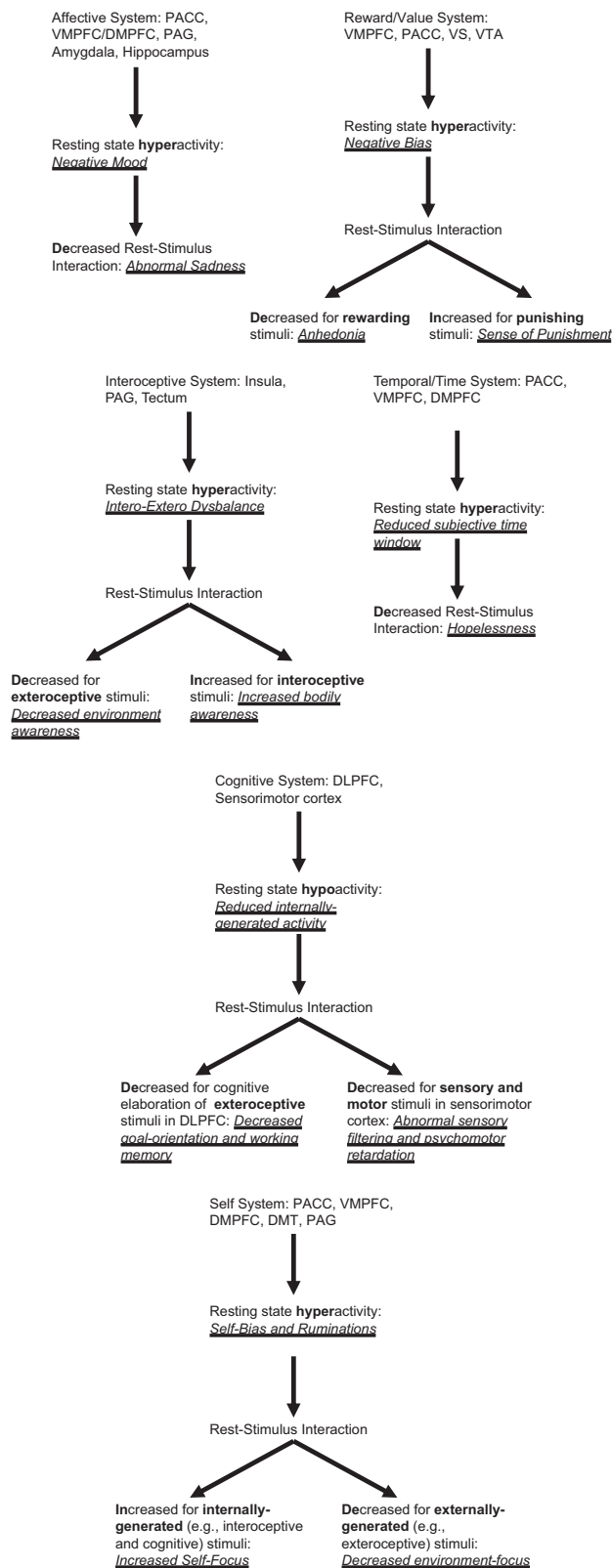


Fig. 3. Resting state activity and psychopathological symptoms.

3.1. Psychopathology I: affective symptoms and reduced rest–stimulus interaction

How does the abnormal resting-state activity impact the neural processing of external stimuli? External stimuli are processed in both lateral cortical and paralimbic–midline regions depending on the respective functional system (affective, reward, sensory, cognitive, etc.). The external stimuli encountering the brain are thus not only confronted with resting-state hypoactivity in the lateral cortical system but, at the time, are also exposed to abnormally elevated resting-state activity in the paralimbic–midline system. This may result in a net effect of reduced external interactions with cognitions, especially in paralimbic–midline systems, for which there is now consistent empirical support.

Functional brain activation studies, especially with emotional stimuli, show predominantly hypoactivity in the PACC, VMPFC and the MOFC (Canli et al., 2004, 2005; Elliott et al., 1998; Mayberg, 2002; Mayberg et al., 1999). More recent fMRI studies have demonstrated predominantly reduced activation in these regions in depression during emotional tasks. Keedwell et al. (2005) demonstrated abnormal signal increases in the PACC, the MOFC and the VMPFC during happy stimuli in depressed patients and lower signal increases in these regions during sad stimuli. Others showed lower MOFC and SUACC decreased signal changes in MDD when exposed to emotional stimuli (Elliott et al., 2002; Kumari et al., 2003; Lawrence et al., 2004; Liotti et al., 2002) whereas higher signal increases were observed in the PACC and VMPFC (Elliott et al., 2002; Fu et al., 2004), which were associated with good treatment responses (Davidson et al., 2003). See also Fitzgerald et al., 2008 for a recent meta-analysis. Taken together, findings during emotional stimulation show reduced stimulus-induced activity especially in anterior cortical midline and paralimbic regions suggesting reduced rest–stimulus interaction.

Other regions showing abnormalities include reward regions like the ventral striatum/nucleus accumbens and the right/left amygdala during positive and/or negative emotional stimulation in MDD (Canli et al., 2004; Kumari et al., 2003; Lawrence et al., 2004; Surguladze et al., 2004). This suggests that changes in both of these regions – the amygdala and the ventral striatum/nucleus accumbens – participate in the abnormally strong negative emotion processing and decreased positive emotion processing in MDD. These regions and other regions of the reward-seeking circuitry like the VMPFC (Heller et al., 2009) may thus be involved in what has been called the “negative bias” which focuses attention on negative emotions, with diminished capacity to sustain and process positive emotions (Heinzel et al., 2009; Mayberg, 2003; Philips et al., 2003).

One of our recent studies directly focussed on rest–stimulus interaction in depression (Grimm et al., 2009a). We found that stimulus-induced activity during emotional stimulation was indeed influenced – with decreased negative BOLD response (deactivation) in those regions with high resting-state mid-cortical activity, e.g., PACC, VMPFC and PCC (for further support, see Sheline et al., 2009). Interestingly, reduced deactivation in these cortical and subcortical regions predicted the degree of depression severity and hopelessness thus establishing direct relationship between reduced rest–stimulus interactions and depression severity (Grimm et al., 2009a).

In addition to changed affective state, rest–stimulus interactions have also been shown to be reduced for rewarding stimuli. The reward-SEEKING system includes subcortical regions like the VTA and the ventral striatum (including the nucleus accumbens) and cortical regions like the ventromedial prefrontal cortex whose neural activity values external stimuli by assigning positive valence to them. And various studies have now shown reduced stimulus-induced activity during reward in depressed patients (Eshel and Roiser, 2010 for a review; Hasler et al., 2009; Heller et al., 2009;

associated negative affect which symptomatically may be over-represented in all other functions, e.g., somatic and cognitive (see Fig. 2c). This may lead to a variety of distinguishable types of MDD, which we will focus on next (see Fig. 3 for schematic overviews).

Kumar et al., 2008; Pizzagalli et al., 2009; Steele et al., 2004). Such decreased stimulus-induced activity is, as before, indicative of reduced rest–stimulus interactions in cortical midline regions.

Interestingly though, there seems to be hyperactivity in the very same regions during punishing stimuli (Eshel and Roiser, 2010 for a review). This is well in line with the symptomatic patterns in depressed patients showing increased guilt and feelings of punishment, while neuronally it suggests increased rather than decreased rest–stimulus interaction for affectively negative inputs. Of course, negative and positive affective networks intermingle in many regions of the brain, including the general trajectory of reward–SEEKING systems through the lateral hypothalamus (Panksepp, 1998). One would consequently assume that the increased resting-state activity in the reward regions, which are not effective in obtaining life-sustaining resources, biases and directs nearby stimulus-induced activity toward a negative affect, and hence punishing, direction. This may account for the negativistic information-processing bias and concurrent anhedonia, the inability to experience pleasure, in depression. This needs to be analyzed in greater detail in future studies.

3.2. Psychopathology II: cognitive symptoms and (Ab)normal reciprocal modulation

In addition to emotional stimuli, imaging studies with external stimuli related to cognitive tasks, such as value judgment, executive functions, and working memory have been investigated. These have yielded reduced activity in especially the DLPFC in depressed individuals which is quite robust (Fitzgerald et al., 2006; Grimm et al., 2008). Reduced stimulus-induced responses in more purely cognitive brain regions like the DLPFC suggests that diminished resting-state activity in these regions may not promote 'psychologically healthy' internal generation of cognitive stimuli for the anticipation of many positive events as commonly occurs in euthymic people. If so, it should be anticipated that there would be reduced rest–stimulus interaction in the lateral cortical regions like the DLPFC also.

Based on these observations, Philips et al. (2003) and Mayberg (2003, 2009) suggest a model of altered reciprocal functional relationship between ventral medial and dorsal lateral prefrontal cortex in MDD. This model of ventral–dorsal dissociation is based predominantly on findings in the resting-state (and only partially on functional activation studies) showing hyperactivity in ventral prefrontal cortex (VMPFC, PACC) and hypoactivity in dorsal prefrontal cortical regions (left DLPFC) in acute MDD (Canli et al., 2004; Davidson et al., 2003; Elliott et al., 1998; Fu et al., 2004; Keedwell et al., 2005; Lawrence et al., 2004; Surguladze et al., 2005), yielding a ventral–dorsal dissociation with abnormal reciprocal modulation, but this remains to be demonstrated in MDD (see below for details).

Such ventral–dorsal dissociation is quite compatible with the more general model of medial–lateral reciprocal modulation, indicating that in normal individuals, stimulus-induced deactivation in medial regions is accompanied by increased activation in the lateral frontal regions and vice versa (Goel and Dolan, 2003; Northoff et al., 2004). Medial deactivation and lateral activation in prefrontal cortex are thus assumed to reciprocally modulate each other during affective and cognitive tasks. This reciprocal modulation has also been shown to be altered – e.g., diminished in depression with chronically increased medial activation (or decreased deactivation) going along with decreased activation in lateral cortex (Bermopohl et al., 2009; Grimm et al., 2008, 2009a).

Stimulus-induced deactivation in medial regions may be abnormally reduced because of both elevated resting-state activity and reduced rest–stimulus interaction. Due to reduced rest–stimulus interaction, the incoming external stimuli may not even get so far into hierarchical processing as to induce deactivations in medial

cortical regions. And if there is concurrently decreased exteroceptive input from other regions, deactivation in medial regions remains diminished from the very beginning, leaving individuals to repeatedly ponder the same issues, over and over, that are troubling them. With regard to diminished reciprocal modulation this means that the system as a whole, can only do what it has always done, to modulate and adapt the activity in lateral regions in repetitive, obsessive ways that does not incorporate new perspectives into working memory.

This also suggests that the apparent abnormality in reciprocal modulation may be an adaptive process, e.g., to account for and adapt the lateral prefrontal cortex to reduced deactivation in medial regions. Hence, what seems to be disturbed (reduced activity of the DLPFC), is largely the manifestation of the normal adaptive function of reciprocal modulation in a different context, e.g., reduced exteroceptive input to both anterior midline and DLPFC regions resulting in reduced neural deactivation in higher social-emotional planning activities of the brain. In other terms, the seemingly abnormal reciprocal modulation is the consequence of a normal functioning mechanism that aims to adapt the brain to a changing context, for example reduced rest–stimulus interaction. The problem in depression is thus not a lesion or abnormality in reciprocal modulation but, to the contrary, the intensification of its normal and adaptive function. In other words, the normal functioning of reciprocal modulation may predispose or enable depressive cognitive dysfunctions including the loss of goal-oriented cognitions.

3.3. Psychopathology III: bodily symptoms and imbalance between intero- and exteroceptive stimulus processing

MDD patients often suffer from generalized bodily symptoms like heart pounding, increased breathing (with yawning), and multiple-diffuse bodily aches. This seems to go along with abnormally increased awareness of their own bodily processes (body perception), including sensitivity to stress and autonomic-vegetative changes as demonstrated in a recent work (Wiebking et al., 2010). The same study also investigated the neuronal activity during exteroceptive and interoceptive awareness (tone and heartbeat counting) in relation to the brain's resting-state activity. Interoceptive stimuli by themselves (e.g., the heartbeat), induced a 'normal' degree of brain signal changes (activation) in the bilateral anterior insula⁴ in depressed patients when considered relative to the preceding resting-state activity levels. This suggests that there is no abnormality in interoceptive stimulus processing.

In contrast to stimulus-induced activity during interoceptive stimuli, however, we observed abnormally reduced activity during exteroceptive stimuli. More specifically, we observed that exteroceptive stimuli induced decreased stimulus-induced activity in the insula in depressed patients when compared to healthy subjects. This let us further question whether such reduced activity is related either to the exteroceptive stimulus itself or rather to differences in the resting-state activity levels. The latter was indeed the case we observed increased resting-state activity in the insula itself, which is well in line with the resting-state hyperactivity in the core–paralimbic system to which the insula belongs.

To test for independent changes in exteroceptively related stimulus-induced activity, we then calculated the exteroceptively related stimulus-induced activity relative to the preceding resting-state activity level. Interestingly, the initially observed difference between healthy and depressed patients in 'absolute', e.g., resting-

⁴ The abnormalities in depression are not confined to the insula but also to typical exteroceptive regions like the visual cortex (see Keedwell et al., 2010; Desseilles et al., 2009; Golomb et al., 2009) which further support our assumption of abnormalities in exteroceptive stimulus processing in depression.

state independent, signal changes during exteroceptive stimuli when calculating them in such 'relative' way, dependent on the preceding resting-state activity level. Hence, when considering this resting-state activity level, there was no difference anymore between healthy and depressed subjects in signal changes during exteroceptive processing.

In contrast to the exteroceptive stimuli, no differences between healthy and depressed subjects were evident in interoceptive stimuli in both relative and absolute signal changes. This difference between intero- and exteroceptive stimuli with regard to relative and absolute signal changes suggests differential interaction of both kinds of stimuli with resting-state activity. Either rest–stimulus interaction is reduced during exteroceptive stimuli or rest–stimulus interaction is increased during interoceptive stimuli which cannot be differentiated on the basis of our findings. What is clear, however, is imbalanced activity between intero- and exteroceptive stimulus processing including their respective interaction with the resting-state activity level. Because of the paucity of work in this area, additional imaging studies need to investigate changes in interoceptive processing in depression.

The study by [Wiebking et al. \(2010\)](#) also investigated psychological measures of body perception, employing the body perception questionnaire (BPQ). They found the BPQ scores to be significantly increased in depressed patients as being indicative of increased bodily awareness. Most interestingly, unlike in healthy subjects, the increased BPQ scores no longer correlated with the signal changes during the resting-state and the exteroceptive condition. This suggests that depressed patients no longer properly modulate their degree of neuronal activity so as to down-modulate the perception and awareness of their own body and to shift attention from the body to the environment. This may help explain the many somatic complaints that characterize MDD. Though tentative, such lack of correlations with abnormally increased neuronal activity has also been seen for other measures of abnormal psychological states like excessive negative affect, self-relatedness problems, and negativistic temporal projections to future possibilities in depression ([Grimm et al., 2009a](#); [Wiebking et al., 2010](#)).

In a subsequent study, [Wiebking et al. \(2010\)](#) also investigated what happens in the DMN, the paracore-midline system, during intero- and exteroceptive stimuli so as to explicitly address the question of how these stimuli interact with the high level of resting-state activity there. Again, they observed no difference in signal changes (deactivation), induced by interoceptive stimuli in the DMN, while they observed decreased deactivation related to exteroceptive stimuli. Hence, in both the insula and the DMN there seems to be decreased neuronal reactivity to exteroceptive stimuli when compared to interoceptive ones.

Taken together, these findings are indicative of an imbalance in the neural processing between intero- and exteroceptive stimuli with only the latter but not the former inducing decreased neural activity. This may consecutively lead to relatively increased neural processing of interoceptive processing and rest–intero interaction when compared to the apparently absolutely reduced exteroceptive processing and rest–extero interaction. As already noted, this abnormal shift toward interoceptive processing may psychopathologically promote increased bodily awareness and subsequent concerns with undesired bodily symptoms. Meanwhile, the decreased exteroceptive processing may be accompanied by reduced awareness of and concern with environmental changes, especially positive events that could beneficially impact depression.

3.4. Psychopathology IV: hopelessness and increased self-focus

A key feature of MDD is hopelessness. Hopelessness is closely related to the sense of time more specifically the ability to extend

ones hopes and expectations into the future (*autonoetic* consciousness, in Endel Tulving's terms). If one is no longer able to extend and project oneself into the future, one no longer is hopeful, focussing on positive life options and possibilities. This well describes MDD. Almost all items in the Beck Hopelessness scale (BHS) monitor one's ability to anticipate positive future events. Recent work highlights elevated scores on the BHS in depressed individuals (see [Grimm et al., 2009a,b](#); [Wiebking et al., 2010](#)). Moreover, these studies found that elevated resting-state activity in the PACC and the VMPFC correlated with the BHS; the higher the resting-state activity in the PACC and VMPFC, the higher were the scores on the BHS, and this relationship was specific for hopelessness rather than other symptoms (see also [Heinzel et al., 2009](#); [Yao et al., 2009](#)).

These findings underscore the psychopathologically specific nature of the relationship of hopelessness with resting-state activity in the VMPFC. This is well in line with observations in healthy subjects where the VMPFC ([Wiebking et al., 2011](#)) and the PACC rather than more posterior midline regions are associated with the extension (slowing) of time in subjective perception, for instance during anticipation or prospection ([Addis et al., 2007](#); [Schacter and Addis, 2007](#); [Schacter et al., 2008](#)). The abnormally elevated resting-state activity in the VMPFC seems to impair anticipation and hence ones experiences of extending hopes into the future. The abnormal resting-state activity level also seems to block the ability of MDD patients' to project hope into the future, thereby promoting hopelessness and ultimately helplessness. Though speculative at this point, this view leads to various hypotheses. For instance, preliminary brain stimulation of the shell of the nucleus in accumbens as an antidepressant, have yielded rapid elevations of planning for pleasant future events ([Schlaepfer et al., 2008](#)).

Let's consider this in a bit more detailed. The above studies evaluated brain signal changes induced by external stimuli in resting-state regions like the PACC and the VMPFC. [Wiebking et al. \(2010\)](#) could even demonstrate that signal changes in the same regions induced by interoceptive stimuli did not correlate with the BHS. This suggests that external stimuli may be specifically related to the extension of the neural (and consecutively experiential) time window. Neurally, this means that the external stimulus may no longer impact the resting-state activity level in the PACC and VMPFC in MDD, leading to what we call reduced stimulus–rest interaction ([Northoff et al., 2010](#)). Thereby, self-related neural processing ([Northoff et al., 2006](#)) may be increasingly constrained to shorter time windows where internally generated stimuli begin to prevail because of diminished impact of external events. Depressed patient may thereby be locked into narrow psychological time windows, which is commonly seen in MDD, further promoting feelings of hopelessness, since one can no longer envision positive future possibilities, but only the sustained limbo of ongoing negative affect and feelings of punishment. The narrowing of the subjective time window may thus lead to an increased focus on one's self coupled with an extremely negative affect.

The symptom of the increased self-focus concerns the heightened awareness of one's self image in depressed patients, even more so since such individuals are no longer absorbed by positive interpersonal interaction, ongoing positive environmental objects and events ([Northoff, 2007](#)). The increased self-focus goes along with the abnormal experiencing of predominantly negative emotions and attribution of negative characteristics (worthlessness) to one's self, which serve as fodder for seemingly endless negativistic ruminations ([Northoff, 2007](#) for details), with little modulation by external events. Convergent evidence from various imaging studies ([Grimm et al., 2009b](#); [Lemogne et al., 2009](#), [2010](#)) has consistently demonstrated diminished signal changes during presentation of either self-related emotional words or emotional pictures, with abnormal activity changes in the anterior

paralimbic–midline regions like the PACC, the VMPFC and the DMPFC.

These anterior paralimbic–midline regions have long been associated with self-related information processing that describes how feelings of personal relevance or meaning are projected onto various external stimuli and internal states (Enzi et al., 2009; Northoff et al., 2006). One would consequently expect that elevated resting-state activity in these brain regions would lead to increased self-related processing and hence to abnormally increased personal concerns in MDD patients. This is exactly what one study found – significantly increased scores for self-relatedness with regard to especially negative emotional pictures (Grimm et al., 2009b).

Since a self-related mental focus is already high during the resting-state, one would expect it to be comparatively (abnormally?) low with regard to external stimuli, with even reduced rest–stimulus interaction, perhaps surprisingly, even perhaps in the case of some highly self-related external stimuli, especially ones that used to be viewed positively. In contrast, internally-generated negative stimuli as related to the abnormally elevated resting-state activity may become salient and be assigned an abnormally high degree of personal relevance as is routinely evident in the obsessive ruminations that MDD patients suffer through. Accordingly, depression is characterized by dysbalanced relations between internally and externally generated stimuli and states of mind with the former being hijacked by negative affect. We postulate that symptomatically this imbalance in rest–stimulus interactions between internally and externally generated stimuli promotes increased self-focus and the diminished influence of positive environmental events.

4. Biochemistry of the resting-state in depression

4.1. Biochemistry I: biochemical modulation of rest–stimulus interaction in healthy subjects

Using combined Magnetic Resonance Spectroscopy (MRS) and fMRI, recent work from our group (Northoff et al., 2007) investigated the level of gamma-aminobutyric acid (GABA) in a typical DMN region, the perigenual anterior cingulate cortex (PACC) which, as part of the DMN, shows predominant Negative Blood Oxygen Level Dependent (BOLD) Response (NBR). The resting-state level of GABA in the PACC correlated with the degree of NBR as induced by an emotional judgment task in the very same region. The higher the resting-state concentration of GABA in the PACC, the higher was the degree of NBR during stimulus-induced activity. This study demonstrated that the resting-state concentration of GABA in the PACC may indeed impact stimulus-induced activity changes in the PACC; this suggests that the resting-state activity level of GABA in a DMN region seems to impact the degree of stimulus-induced activity in the same region.

Another study in healthy subjects investigated the resting-state concentration of GABA in the visual cortex and its effects on subsequent stimulus-induced activity in the visual cortex itself and gamma frequency bands (Muthukumaraswamy et al., 2009). They measured resting-state levels of GABA in the visual cortex with MRS and employed fMRI and magnetoencephalography (MEG) to measure stimulus-induced activity changes in the visual cortex. The resting-state concentration of GABA in the visual cortex predicted the degree of stimulus-induced activation (positive BOLD response) and elevated gamma frequency power in the same brain region.

Despite focusing on different regions, i.e., PACC and visual cortex, both studies observed predicted stimulus-induced activity changes in the resting-state by levels of GABA. In contrast, resting-state levels of glutamate, the predominant excitatory transmitter of the brain, were not related to rest–stimulus interactions. This suggests that the resting-state concentration of GABA as

the major inhibitory transmitter may have a crucial role in linking resting-state activity to stimulus-induced activity thereby mediating aforementioned rest–stimulus interactions in the DMN (Northoff et al., 2010).

Taken together, these initial findings suggest that GABA-ergic mediated neuronal inhibition may be crucial in enabling and predisposing the linkage of the resting-state activity of a particular region to its activity changes during stimulation by an external stimulus. In short, GABA-ergic modulation may be crucial in normal rest–stimulus interactions, albeit the mechanism is by no means clear. Additional work is needed to illuminate how neuronal inhibition by GABA mediates the relationship between resting-state and stimulus-induced activity within Default Mode Networks.

While GABA may be crucial in rest–stimulus interaction, the biochemical modulation of the resting-state activity by itself, independent of stimulus-induced activity, remains unclear. Glutamate has been proposed as a key mediator of the metabolic energetics of the resting-state (Raichle and Mintun, 2006; Shulman et al., 2004, 2007; van Eijsden et al., 2009), but precise causal hypotheses remain to be proposed. Recent data from our group (Enzi et al., 2009, Duncan et al. submitted) suggest that concentrations of glutamate are directly related to the resting-state activity level in the PACC, a region with typically high resting-state activity. Importantly, unlike for GABA, this relationship was not observed during stimulus-induced activity. Tentatively, we propose that glutamate maintains and modulates the resting-state activity level itself while GABA enables the transition from the resting-state to stimulus-induced activity (rest–stimulus interaction).

4.2. Biochemistry II: biochemical modulation of rest–stimulus interaction in depressed subjects

GABA is the brain's major inhibitory transmitter and, as described above, play a major role in mediating rest–stimulus interaction. Thus, one could predict changes in GABA in MDD, which is indeed the case. Although studies of brain GABA in living human brains are scarce, there is evidence for both reduced and normal intra- and extracellular concentrations in paralimbic and midline regions like the PACC and the DMPFC as well as in lateral regions like the occipital cortex (Bhagwagar et al., 2007; Hasler et al., 2007; Maciag et al., 2010; Sanacora et al., 1999, 2004).

Post-mortem findings report deficits in the GAD, glutamate decarboxylase-67 the enzyme that converts glutamate into GABA (Rajkowska et al., 2007). There is further evidence from two post-mortem studies for GABA-ergic abnormalities; they show that the mRNA expression of specific subunits of the GABA-A receptor (e.g., alpha 1,3,4, and delta) are reduced in cortical and subcortical regions in depressed suicide victims (Merali et al., 2004; Poulter et al., 2008, 2010; see also Sequeira et al., 2007, 2009 for genetic expression of GABA). Finally, animal studies demonstrate decreased GABA concentration and reduced GABA-A/B receptor sensitivity and expression in many paralimbic and midline cortical regions as well as in subcortical core–paracore regions (Alcaro et al., 2010). Taken together, these findings lead us to consider that there may be decreased GABA-mediated neural inhibition in cortical and subcortical regions of the 'inner and middle rings' described earlier.

The crucial role of GABA and GABA-ergic inhibition in depression is further corroborated by results from Transcranial Magnetic Stimulation (TMS). TMS allows measurement of resting-state activity in terms of neural inhibition in techniques like 'silent period' and 'paired pulse' techniques. Severely depressed MDD patients show deficits in both measures in motor cortex which is indicative of a deficit of cortical inhibition as mediated by both GABA-A and GABA-B receptors (Bajbouj et al., 2005a,b; Levinson et al., 2010; see also Sanacora, 2010 for commentary). One should be aware though that

these studies concern the motor cortex and as part of the outer ring, the lateral cortical regions. What would be needed are studies testing cortical excitability in paralimbic and midline regions, which are very difficult to reach with TMS.

In addition to GABA, glutamate is the other major neurochemical player within the cortex and unlike GABA, is predominantly excitatory rather than inhibitory (see above). In human MDD studies, reduced levels of glutamate/glutamine as measured with MRS were observed in regions like the DMPFC, the hippocampus, the PACC, and the occipital cortex (Alcaro et al., 2010; Hasler et al., 2007; Price and Drevets, 2010; Sanacora et al., 1999; Walter et al., 2009). Animal models of depression have also exhibited abnormal concentrations of glutamate in these regions (and other subcortical regions like the raphe nuclei) and, quite consistently abnormal upregulation of the NMDA-receptor and down-regulation of the AMPA- and GluR2 receptors in various cortical paralimbic and subcortical core–paracore regions (Alcaro et al., 2010).

The crucial role of NMDA-receptors is further supported by recent studies showing that the NMDA-receptor antagonist ketamine can reverse pretreatment hyperfunction of the PACC during either emotional or cognitive tasks (Salvadore et al., 2009, 2010). Unfortunately though, imaging of NMDA-receptors in human MDD remains to be reported. Other components of glutamatergic transmission like the glutamate transporter and glutamate synthetase have also been observed to be abnormal in MDD (Banar et al., 2010; Walter et al., 2009). Taken together, these results suggest abnormal glutamate-mediated neural excitation in subcortical–cortical regions of the inner and middle rings, the core–paracore, the limbic as well as paralimbic/cortical midline regions.

Taken together, these findings strongly suggest abnormal balances between glutamate- and GABA-ergic inhibition and excitation in the paralimbic–midline and core–paracore regions in MDD. The net effect of such imbalances may be decreased neural inhibition and thus increased neural excitation in the inner and middle ring at both cortical and subcortical levels. This raises the question for the relationship between resting-state hyperactivity and increased neural excitation in these regions, a question not yet addressed. One recent studies in humans (Walter et al., 2009) observed that decreased negative BOLD response (NBR) in the PACC as being indicative of increased resting-state activity was decoupled from GABA while, at the same time, being abnormally related to the level of glutamate. This suggests that the abnormally high level of the resting-state activity in the PACC may be mediated by increased neural excitation due to glutamate. However, these results are tentative and the exact relationship between glutamate and resting-state activity remain unclear in both healthy and depressed subjects.

Finally, the question for the relationship of GABA/glutamate to serotonin deserves attention, especially since serotonin is the most studied player in the genesis of depression. There is abundant evidence for serotonergic abnormalities in MDD, including synaptic levels of serotonin and specific serotonergic receptors (5HT-1a, 5HT-1b, etc.) in subcortical core–paracore and cortical paralimbic–midline regions (see Drevets et al., 2008a,b as well as Savitz and Drevets, 2009b for a review of the genetic side), and how that is related to GABA and glutamate transmission. GABA- and glutamatergic neuron systems are ubiquitous throughout the whole cortex and in most subcortical regions. This distinguishes them from more specific neuromodulatory systems like serotonergic and adrenergic–noradrenergic systems, whose neurons are situated in subcortical core–paracore regions (raphe nuclei, locus coeruleus) and are connected via long axons to forebrain–limbic regions as well as paralimbic and midline regions in especially anterior parts of the cortex like the VMPFC and the PACC (Morgane et al., 2005). However, serotonergic neurons are connected to GABA-ergic

interneurons on both subcortical and cortical levels which may suggest that alterations in the one, for example the serotonergic systems, entails changes in the other, for example GABA- and glutamatergic systems.

4.3. Biochemistry III: a unified subcortical–cortical biochemical resting-state hypothesis

How can we integrate GABA–glutamatergic abnormalities with the serotonergic–adrenergic/noradrenergic abnormalities in MDD? Serotonergic neurons transmit to GABA-ergic interneurons within raphe nuclei as well as at cortical levels, especially within the PACC and the VMPFC (Morgane et al., 2005). GABA-ergic neurons being predominantly interneurons modulate glutamatergic neurons that connect one cortical region with another. This means that for instance serotonergic neurons probably directly inhibit GABA-ergic transmission which in turn may disinhibit glutamatergic neurons. While preliminary, this suggests some linkages between anatomy and biochemistry in MDD, and hence would suggest the following preliminary model.

Subcortical mesencephalic core–paracore regions show resting-state hyperactivity, a robust finding, currently based largely on animal data (Alcaro et al., 2010). Abnormally elevated resting-state hyperactivity in subcortical core–paracore regions may be related to abnormal function of the neuromodulatory systems located in the raphe nucleus and the locus coeruleus with serotonin and adrenaline/noradrenaline (and other transmitters like dopamine, and acetylcholine; see Drevets et al., 2008a for an excellent review). Due to their ascending fibres to the limbic forebrain and the cortex, the elevated resting-state activity from subcortical core–paracore regions is quasi transferred to cortical regions leading to the well-established resting-state hyperactivity in paralimbic and midline regions.

How is this subcortical–cortical transfer of elevated resting-state activity mediated on the biochemical level? Since the ascending serotonergic and adrenergic–noradrenergic connections connect on GABA-ergic interneurons on the cortical level, the latter may aim to adapt to the abnormal subcortical input by down-tuning neural inhibition. This in turn leads to decreased GABA-ergic inhibition of glutamatergic-mediated cortico-cortical connections with the net effect of increased neural excitation. Increased neural excitation may then spread along established anatomical lines to other regions with the subsequent spread of the abnormally elevated resting-state activity from subcortical core–paracore to cortical paralimbic–midline regions.

At the same time though, inner-middle and outer cortical rings seem to stand in a relationship of reciprocal modulation (see above for details). This means that inner-middle and outer activity seem to reciprocally balance each other with hyperactivity in the former inducing consecutively hypoactivity in the latter. This may result in decreased resting-state activity in the lateral cortical regions in depression (Bermphol et al., 2009; Mayberg, 2003 for support; 2009). One should note that decreased lateral resting-state activity is not due to abnormal function of reciprocal modulation but rather due to its preserved function that adapts the lateral outer cortex to the level of function in the inner-middle paralimbic–midline cortex. Accordingly, neuronal mechanisms like reciprocal modulation may become skewed, leading to abnormally elevated paralimbic–midline resting-state activity.

How are the psychopathological symptoms related to the different biochemical mechanisms discussed here? Depending on the respective system and anatomical locations, one may assume particular biochemical modulation of specific depressive symptoms. Neuronal systems processing affect and emotion are located predominantly subcortically in the core–paracore regions and the limbic system (Panksepp, 1998) where a diversity of neuropeptides

provide affective specificity, albeit all systems are fully exposed to ascending biogenic amine influences – of serotonin, noradrenaline and dopamine (at least in humans where dopamine fibres extend further back toward sensory-perceptual areas, as opposed to just frontal-executive regions in most mammals), and to a lower extent adrenaline and histamine. One would consequently expect the affective symptoms in depression to be regulated by these transmitters, in terms of arousal, but perhaps not specific valence.

The valence modulation of affect may be left to various neuropeptides that have more specific emotional-affective functions in the brain (Panksepp and Harro, 2004). In addition, more widespread neuropeptides such as endogenous opioids, which figure in practically every aspect of positive-hedonics in the brain, including social ones from sexuality to play, may be central in MDD symptoms. The profound alleviation of separation-distress by opioids, which may be a major source of psychic pain (Panksepp, 2006; Panksepp and Watt, in press), would suggest that opiate receptor agonists could be harnessed as useful anti-depressants, and the relatively safe agonist/antagonist buprenorphine, at incredibly low doses, is highly effective in people where all other treatment modalities have failed (Bodkin et al., 1995). What remains unclear though is how the specific and widespread neuropeptides interact with GABA and glutamate on subcortical and cortical levels of affective processing. This may be crucial in better understanding the exact anatomical–biochemical mechanisms of specific depressive symptoms.

In contrast, other symptoms like increased self-focus and hopelessness may be rather related to GABA and glutamate as the dominating substances on the cortical level. Hence, the anatomical location of the functional system supposedly underlying the psychopathological symptom in question may provide some hint about the biochemical modulation of the latter. However, to assume such biochemical–psychopathological linkage remains speculative at this point.

5. “Resting-state hypothesis” as unifying hypothesis for MDD

We have outlined and presented the ‘Resting-state – Emotional systems Hypothesis’ as a tentative attempt to provide a unifying and overarching pathophysiological framework of MDD. Thereby, based on the data, we suggest that the resting-state hypothesis can bridge the gap from the level of symptoms and psychopathology over the anatomical and biochemical levels to the genetic-molecular levels. If so the resting-state hypothesis as a large-scale, hierarchical neural hypothesis may serve as unifying and overarching framework for the pathophysiology of MDD. We have focused on the anatomical, functional-psychological and biochemical basis of the resting-state activity. For the time being, this leaves out many other dimensions in depression like the genetic, the immunological, the social, the clinical, and the endocrine. While not extensively covering all these issues here, we would at least briefly address them (see also Fig. 4).

5.1. Resting-state hypothesis I: unification of different levels

Can our resting-state hypothesis account for the aforementioned heterogeneity of symptoms, systems, regions, and biochemistries? The conceptualization of human anatomy in terms of concentric and radial layers provided a model that allowed integrate subcortical and cortical function within a unified framework. And the patterns of hyper- and hypoactive resting-state activity in MDD seem to follow these concentric and radial layers at both subcortical and cortical levels. Hence, a focus on resting-state activity may provide a unifying framework for the heterogeneity of inter-

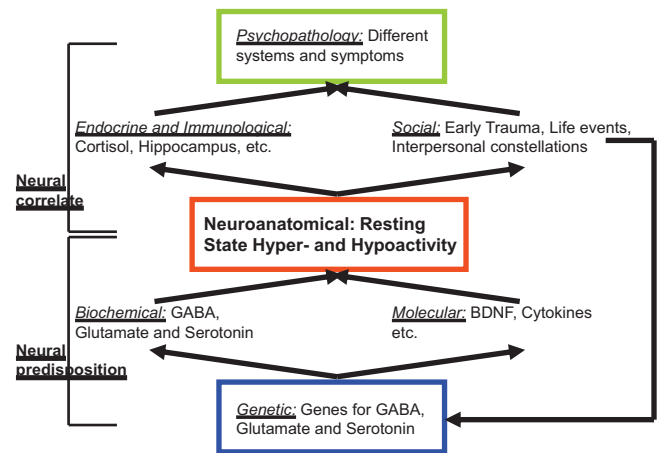


Fig. 4. Different levels of the resting state hypothesis in depression.

acting brain regions; as such the resting-state hypothesis must be considered a predominantly *neuro-anatomical hypothesis*.

Furthermore, we were able to link the abnormal resting-state patterns to different biochemical systems to GABA- and glutamatergic systems on the cortical level and to serotonergic- and adrenergic–noradrenergic systems on the subcortical level with the latter providing the link to the former. Hence, anatomical integration seemed to be accompanied by biochemical integration thus accounting for the heterogeneity of biochemistry; our resting-state hypothesis may thus be considered a *neuro-biochemical hypothesis*.

While focusing here on predominantly anatomical and biochemical levels and their linkage to the various symptoms, we do claim that especially our biochemical considerations open the door for being connected to the genetic-molecular levels of analysis. Also, candidate genes would be, for instance, those that are implicated in GABA and glutamate that are presumably the major players in enabling the resting-state activity level and rest–stimulus interaction (see above). However, equally important, would be to show the interaction between GABA/glutamate and serotonin, and a host of neuropeptides, not only biochemically but also on the genetic level. In the future, this could transform the so far rather neurobiochemical resting-state hypothesis into a truly *neuro-genetic hypothesis*.

This was followed by consideration of the relationship of abnormal resting-state activity patterns to the various psychopathological symptoms, not only at lower core levels of the brainstem (as noted above) but also within the emotion-cognition integration regions of medial frontal regions. This latter psychological linkage made the consideration of rest–stimulus interaction necessary. While no direct data are currently available, indirect evidence showed that abnormalities in rest–stimulus interactions could well account for the various symptoms observed in MDD. Hence, the resting-state hypothesis assumes that the symptoms in MDD are not caused themselves by the abnormal resting-state activity but are rather related to the consequences or effects of the resting-state activity on the neural processing of subcortical emotional, interoceptive-affective and diverse external stimuli. Since these consequences or effects are so widespread crossing different regions and functional systems along the lines of the delineated subcortical–cortical systems, they go along with the induction of an equal heterogeneity of symptoms. If the transition from the abnormal resting-state activity over rest–stimulus interaction to the various depressive symptoms could be elaborated and detailed in the future, the resting-state hypothesis has the potential to become a truly *neuro-psychopathological hypothesis*, a view that is currently lacking in the field.

Future and more detailed investigation of the transition from normal resting-state activity to rest–stimulus interactions and stimulus-induced activity studies may also yield insight into the various functions and mechanisms impacting such transitions. One factor crucial here may be social factors as for instance loss, trauma as well as specific interpersonal vicissitudes, especially early social loss (Heim and Nemeroff, 1999) that are well known to trigger depressive episodes. Indeed, a functional emotional-systems view, that may be concordant with the above view, has been advanced (Panksepp and Watt, in press).

If these various social factors could be shown to impact either the resting-state level itself or the degree of rest–stimulus interaction, the resting-state hypothesis could become a *neuro-social hypothesis*. Investigation of the social factor may also be mediated by endocrine and immunological function which then in turn may impact the resting-state activity and rest–stimulus interaction. This means that our resting-state hypothesis would then open its doors for *neuro-immunological* and *neuro-endocrine hypotheses*.

5.2. Resting-state hypothesis II: endophenotypes and biomarkers

The term ‘endophenotype’ describes an internal intermediate phenotype that bridges the gap between the genetic equipment to some physiological or psychological markers of the disease (Gottesman and Shields, 1973; Gottesmann and Gottesman, 2007; Hasler et al., 2004). As such the concept of the endophenotype focuses predominantly on genetic and quite simple behavioral factors (see Hasler et al., 2006 for criteria) which, though neglected here, can readily be linked to the present analysis. For instance, the subcortical primary-process emotional systems provide unique and psychologically relevant endophenotypic networks (Panksepp, 2006) potentially critical importance for the affective qualities of depression (Panksepp and Watt, in press). However, as indicated, we assume the genetic underpinnings of the predisposition to develop abnormally elevated resting-state activity in subcortical affective symptoms under certain circumstances, be they social or biological, to be even deeper endophenotypes, but that level of analysis remain unclear for now. Since, as demonstrated above, GABA and glutamate seem to be key player in adjusting and modulating the actual level of the resting-state activity, several key genes may be related to such functions at various levels of the neuroaxis. For instance, at the midbrain level, the most affectively intense networks of the PAG, exhibit some gene expression changes in robust animal models of depression (e.g., Krishnan and Nestler, 2008; Kroes et al., 2007).

One may also want to raise the question for the origin or cause of the increased resting-state activity in paralimbic–midline regions in depression. There is much debate these days about whether depression is a neurodevelopmental or neurodegenerative disorder with the final verdict remaining open (see Drevets et al., 2008a for a recent overview). One may hypothesize that the traumatic event itself and thus the early object loss (Bowlby, 1980; Watt and Panksepp, 2009) may be crucial in enabling and predisposing the abnormal elevation of the paralimbic–midline resting-state activity in depression. Subjects at risk for depression seem to also show a tendency toward increased paralimbic–midline resting-state activity (see Mayberg, 2009; Price and Drevets, 2010 for recent reviews) which would at least indirectly support our assumption.

By bridging the gap from the molecular-genetic over the anatomical and biochemical to the psychopathological, symptomatic level, MDD-characteristic changes in resting-state may have the potential to serve as a provocative ‘endophenotype’ of diagnostic relevance. The concept of endophenotype has been introduced to describe criteria that can relate behavior and symptoms to the genetic level. Our resting-state hypothesis may be such endophenotype with much genetic research especially

in remitted patients and non-affected relatives that could be done.

Let us consider this possibility in some more detail. The concept of the endophenotype seems to imply that the marker in question is a sufficient condition of the symptoms. Resting-state hyperactivity, along with imbalances in subcortical emotional systems, may be a sufficient condition for depressive feelings and thus, when intense, may constitute what is often called ‘neural correlate’ of depressive symptoms like anhedonia, sadness, etc. This however is to miss the distinction between resting-state activity itself and rest–stimulus interaction. The abnormal resting-state activity may lead to abnormal rest–stimulus interaction which may then induce the various symptoms. Hence, it is the abnormal rest–stimulus interaction rather than the abnormal resting-state activity alone that may be regarded the sufficient condition of depression and its various symptoms.

Abnormal resting-state activity itself, in contrast, may by itself not be sufficient to induce clinically significant depressive symptoms although it may characterize normal sadness and grief. However, without abnormal resting-state activity, perhaps abnormal rest–stimulus interactions could not occur so that the former must be regarded a necessary rather than sufficient condition of depression. Hence, abnormal resting-state activity may be considered what can be called ‘neural predisposition’ – a susceptibility marker – that describes necessary but non-sufficient conditions and thus what clinically is called a ‘risk factor’. The characterization of resting-state activity as a neural predisposition – a neural correlate – would distinguish it from abnormal rest–stimulus interactions as the final cause of depression. In any event, perhaps certain abnormal resting-state activities, as endophenotypic neural predispositions, may highlight certain commonly shared characteristics of the whole depression-related neural continuum. In contrast, the various rest–stimulus interactions may be biomarkers for more specific functional systems and their respective symptoms. Hence, what we here call ‘neural predisposition’ may, in pathophysiological terms, correspond to the concept of endophenotypes within the clinical context. The resting-state ‘neural correlates’ may then be reflecting what are clinical called biomarkers.

6. Conclusion

We have focused on the abnormalities of resting-state activity across different regions in MDD. Thereby we put the current findings of resting-state hyper- and hypo-activity into a wider neuroanatomical context which suggests multiple radial-concentric and vertical integrations between subcortical and cortical regions. The inner-middle ring of subcortical core–paracore and cortical paralimbic–midline regions shows abnormal resting-state hyperactivity in MDD while the outer ring of the lateral subcortical and lateral cortical region is relatively hypoactive. Since the different subcortical–cortical systems, e.g., the different rings, include different functional systems as for affect, bodily perception, reward, cognition, etc. abnormal resting-state activity leads to abnormal rest–stimulus interaction and consecutively to the different kinds of symptoms in MDD.

Both the abnormal resting-state activity itself and the abnormal rest–stimulus interaction may be associated with specific biochemical mechanisms, the former especially with subcortical serotonin and cortical glutamate while the latter may be associated with GABA–serotonin and GABA–glutamate interaction. These higher integrative systems are strongly ‘motivated’ and ‘affected’ by diverse subcortical emotional and motivational systems, not fully developed here but exhaustively discussed elsewhere (Panksepp, 1998; Watt and Panksepp, 2009). Since our full ‘Resting-state hypothesis’ can be specified not only in anatomical, psychopatho-

logical and biochemical terms, but also connected to other relevant dimensions, including genetic, social, endocrine and immunological ones, it may be regarded a unifying and overarching hypothesis. As such it is well suited to appropriately account for MDD as a widely represented brain somatic-cognitive-affective systems disorder.

Characterized in this way, depression may be compared to other broad systems disorders like multiple sclerosis (MS) or diabetes mellitus (DM). Demyelination is considered one of the main factors in MS which can penetrate the whole brain and thus all of its various sub-systems. Demyelination is the neural predisposition and its penetration into different functional systems, with various sensory, motor and autonomic changes being the neural consequences. Hence, demyelination may be regarded analogous to the abnormally elevated resting-state activity whose effects on rest-stimulus interaction in the different functional systems for affect, cognition, body, etc. may correspond to the manifestation of demyelination in specific systems or consider diabetes mellitus. There is abnormally high sugar, as a result of low insulin, which metaphorically corresponds well to the abnormally elevated resting-state activity in MDD as potentially due to GABA-glutamate imbalances. Just as the abnormally high blood sugar in diabetes interacts with the biochemical mechanisms in all of the different bodily organs, e.g., eyes, feet, etc. the elevated brain resting-state may have comparable effects on diverse brain-mind subsystems. As a result of such interaction, diabetic patients often suffer from different symptoms like becoming blind or gangrene in extremities, which metaphorically can be seen to resemble the various abnormal rest-stimulus interactions we have described in the different functional sub-systems of the brain.

In sum, though tentative, our resting-state hypothesis may allow to bridge the gap between basic neuroscientific findings and clinical psychopathology. Moreover, the resting-state hypothesis regards MDD as broad-scale system disorder that affects various functional networks in the brain, especially those related to our core emotional values, thereby re-integrating subcortical and cortical systems in abnormal ways. Finally, by making the distinction between neural predisposition and neural correlates our resting-state hypothesis bridges the gap from the etiological to symptomatic levels. This may promote refined linkages of pathophysiological hypothesis to the clinical manifestations where the distinction between neural predisposition and neural correlates is mirrored in ways that resemble endophenotypes and biomarkers in modern biological psychiatry.

Acknowledgments

The work was supported by grants to G. Northhoff. and J. Panksepp from the Hope of Depression Research Foundation (HDRF), and G. Northhoff from the German Research Foundation DFG/SFB 776 A6, the EJLB Michael Smith Foundation, and CRC Canada Research Chair.

References

- Addis, D.R., Wong, A.T., Schacter, D.L., 2007. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377.
- Alcaro, A., Panksepp, J., Witzak, J., Hayes, D.J., Northhoff, G., 2010. Is subcortical-cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach. *Neurosci. Biobehav. Rev.* 34, 592–605.
- Anisman, H., 2009. Cascading effects of stressors and inflammatory immune system activation: implications for major depressive disorder. *J. Psychiatry Neurosci.* 34, 4–20.
- Bajbouj, M., Brakemeier, E.L., Schubert, F., Lang, U.E., Neu, P., Schindowski, C., Danker-Hopfe, H., 2005a. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex and cortical excitability in patients with major depressive disorder. *Exp. Neurol.* 196, 332–338.
- Bajbouj, M., Lang, U.E., Neu, P., Heuser, I., 2005b. Therapeutic brain stimulation and cortical excitability in depressed patients. *Am. J. Psychiatry* 162, 2192–2193.
- Banasr, M., Chowdhury, G.M., Terwilliger, R., Newton, S.S., Duman, R.S., Behar, K.L., Sanacora, G., 2010. Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. *Mol. Psychiatry* 15, 501–511.
- Berpohl, F., Walter, M., Sajonz, B., Lucke, C., Hagele, C., Sterzer, P., Adli, M., Heinz, A., Northhoff, G., 2009. Attentional modulation of emotional stimulus processing in patients with major depression – alterations in prefrontal cortical regions. *Neurosci. Lett.* 463, 108–113.
- 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.
- Bodkin, J.A., Zornberg, G.L., Lukas, S.E., Cole, J.O., 1995. Buprenorphine treatment of refractory depression. *J. Clin. Psychopharmacol.* 15, 49–57.
- Bowlby, J., 1980. *Loss: Sadness and Depression*. Basic Books, New York.
- 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.
- Canli, T., Cooney, R.E., Goldin, P., Shah, M., Sivers, H., Thomason, M.E., Whitfield-Gabrieli, S., Gabrieli, J.D., Gotlib, I.H., 2005. Amygdala reactivity to emotional faces predicts improvement in major depression. *Neuroreport* 16, 1267–1270.
- Canli, T., Sivers, H., Thomason, M.E., Whitfield-Gabrieli, S., Gabrieli, J.D., Gotlib, I.H., 2004. Brain activation to emotional words in depressed vs healthy subjects. *Neuroreport* 15, 2585–2588.
- Carhart-Harris, R.L., Friston, K.J., 2010. The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain* 133, 1265–1283.
- Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., Schooler, J.W., 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc. Natl. Acad. Sci. U.S.A.* 106, 8719–8724.
- Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am. J. Psychiatry* 160, 64–75.
- de Greck, M., Rotte, M., Paus, R., Moritz, D., Thiemann, R., Proesch, U., Bruer, U., Moerth, S., Tempelmann, C., Bogerts, B., Northhoff, G., 2008. Is our self based on reward? Self-relatedness recruits neural activity in the reward system. *NeuroImage* 39, 2066–2075.
- de Olmos, J.S., Heimer, L., 1999. The concepts of the ventral striatopallidal system and extended amygdala. *Ann. N. Y. Acad. Sci.* 877, 1–32.
- Desseilles, M., Balteau, E., Sterpenich, V., Dang-Vu, T.T., Darsaud, A., Vandewalle, G., Albouy, G., Salmon, E., Peters, F., Schmidt, C., Schabus, M., Gais, S., Degueldre, C., Phillips, C., Luxen, A., Anseau, M., Maquet, P., Schwartz, S., 2009. Abnormal neural filtering of irrelevant visual information in depression. *J. Neurosci.* 29, 1395–1403.
- Drevets, W.C., Price, J.L., Furey, M.L., 2008a. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* 213, 93–118.
- Drevets, W.C., Savitz, J., Trimble, M., 2008b. The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrosc.* 13, 663–681.
- Elliott, R., Rubinsztein, J.S., Sahakian, B.J., Dolan, R.J., 2002. The neural basis of mood-congruent processing biases in depression. *Arch. Gen. Psychiatry* 59, 597–604.
- Elliott, R., Sahakian, B.J., Michael, A., Paykel, E.S., Dolan, R.J., 1998. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. *Psychol. Med.* 28, 559–571.
- Enzi, B., de Greck, M., Prosch, U., Tempelmann, C., Northhoff, G., 2009. Is our self nothing but reward? Neuronal overlap and distinction between reward and personal relevance and its relation to human personality. *PLoS One* 4, e8429.
- Eshel, N., Roiser, J.P., 2010. Reward and punishment processing in depression. *Biol. Psychiatry* 68, 118–124.
- Feinberg, T.E., 2009. *From Axons to Identity: Neurological Explorations of the Nature of the Self*, 1st ed. W.W. Norton & Company, August 3, 2009.
- Fitzgerald, P.B., Laird, A.R., Maller, J., Daskalakis, Z.J., 2008. A meta-analytic study of changes in brain activation in depression. *Hum. Brain Mapp.* 29, 683–695.
- 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, 33–34.
- Friston, K., 2010. The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11, 127–138.
- Fu, C.H., Williams, S.C., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., Pich, E.M., Williams, P.M., Reed, L.J., Mitterschiffthaler, M.T., Suckling, J., Bullmore, E.T., 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* 61, 877–889.
- Goel, V., Dolan, R.J., 2003. Reciprocal neural response within lateral and ventral medial prefrontal cortex during hot and cold reasoning. *NeuroImage* 20, 2314–2321.
- Golomb, J.D., McDavitt, J.R., Ruf, B.M., Chen, J.J., Saricicek, A., Maloney, K.H., Hu, J., Chun, M.M., Bhagwagar, Z., 2009. Enhanced visual motion perception in major depressive disorder. *J. Neurosci.* 29, 9072–9077.
- Gottesman, I.I., Shields, J., 1973. Genetic theorizing and schizophrenia. *Br. J. Psychiatry* 122, 15–30.
- Gottesmann, C., Gottesman, I., 2007. The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. *Prog. Neurobiol.* 81, 237–250.
- Greicius, M.D., Flores, B.H., Menon, V., Glover, G., Solvason, H.B., Kenna, H., Reiss, A.L., Schlaggar, A.F., 2007. Resting state functional connectivity in major depres-

- sion: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol. Psychiatry* 62, 429–437.
- Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., Northoff, G., 2008. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol. Psychiatry* 63, 369–376.
- 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, 932–939.
- 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.
- Harro, J., Orelund, L., 2001. Depression as a spreading adjustment disorder of monoaminergic neurons: a case for primary implications of the locus coeruleus. *Brain Res. Rev.* 38, 79–128.
- Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., Manji, H.K., 2006. Toward constructing an endophenotype strategy for bipolar disorders. *Biol. Psychiatry* 60, 93–105.
- Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29, 1765–1781.
- Hasler, G., Luckenbaugh, D.A., Snow, J., Meyers, N., Waldeck, T., Geraci, M., Roiser, J., Knutson, B., Charney, D.S., Drevets, W.C., 2009. Reward processing after catecholamine depletion in unmedicated, remitted subjects with major depressive disorder. *Biol. Psychiatry* 66, 201–205.
- Hasler, G., van der Veen, J.W., Tuminis, 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.
- Heim, C., Nemeroff, C.B., 1999. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol. Psychiatry* 46, 1509–1522.
- Heimer, L., 2003. A new anatomical framework for neuropsychiatric disorders and drug abuse. *Am. J. Psychiatry* 160, 1726–1739.
- Heinzel, A., Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Boeker, H., Northoff, G., 2009. Segregated neural representation of psychological and somatic-vegetative symptoms in severe major depression. *Neurosci. Lett.* 456, 49–53.
- Heller, A.S., Johnstone, T., Shackman, A.J., Light, S.N., Peterson, M.J., Kolden, G.G., Kalin, N.H., Davidson, R.J., 2009. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. *Proc. Natl. Acad. Sci. U.S.A.* 106, 22445–22450.
- Keedwell, P.A., Drapier, D., Surguladze, S., Giampietro, V., Brammer, M., Phillips, M., 2010. Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. *J. Affect. Disord.* 120, 120–125.
- Keedwell, P.A., Andrew, C., Williams, S.C., Brammer, M.J., Phillips, M.L., 2005. The neural correlates of anhedonia in major depressive disorder. *Biol. Psychiatry* 58, 843–853.
- 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.
- Kumar, P., Waite, G., Ahearn, T., Milders, M., Reid, I., Steele, J.D., 2008. Abnormal temporal difference reward-learning signals in major depression. *Brain* 131, 2084–2093.
- Kumari, V., Mitterschiffthaler, M.T., Teasdale, J.D., Malhi, G.S., Brown, R.G., Giampietro, V., Brammer, M.J., Poon, L., Simmons, A., Williams, S.C., Checkley, S.A., Sharma, T., 2003. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biol. Psychiatry* 54, 777–791.
- Lawrence, N.S., Williams, A.M., Surguladze, S., Giampietro, V., Brammer, M.J., Andrew, C., Frangou, S., Ecker, C., Phillips, M.L., 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol. Psychiatry* 55, 578–587.
- Lemogne, C., Bergouignan, L., Piolino, P., Jouvent, R., Allilaire, J.F., Fossati, P., 2009. Cognitive avoidance of intrusive memories and autobiographical memory: specificity, autothetic consciousness, and self-perspective. *Memory (Hove, England)* 17, 1–7.
- Lemogne, C., Mayberg, H., Bergouignan, L., Volle, E., Delaveau, P., Lehericy, S., Allilaire, J.F., Fossati, P., 2010. Self-referential processing and the prefrontal cortex over the course of depression: a pilot study. *J. Affect. Disord.* 124, 196–201.
- Levinson, A.J., Fitzgerald, P.B., Favalli, G., Blumberger, D.M., Daigle, M., Daskalakis, Z.J., 2010. Evidence of cortical inhibitory deficits in major depressive disorder. *Biol. Psychiatry* 67, 458–464.
- Liotti, M., Mayberg, H.S., McGinnis, S., Brannan, S.L., Jerabek, P., 2002. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. *Am. J. Psychiatry* 159, 1830–1840.
- Liotti, M., Panksepp, J., 2004. On the neural nature of human emotions and implications for biological psychiatry. In: J. P. (Ed.), *Textbook of Biological Psychiatry*. Wiley, New York, pp. 33–74.
- Maciag, D., Hughes, J., O'Dwyer, G., Pride, Y., Stockmeier, C.A., Sanacora, G., Rajkowska, G., 2010. Reduced density of calbindin immunoreactive GABAergic neurons in the occipital cortex in major depression: relevance to neuroimaging studies. *Biol. Psychiatry* 67, 465–470.
- MacLean, P.D., 1990. *The Triune Brain in Evolution: Role in Paleocerebral Functions*. Plenum Press, New York.
- Mällo, T., Matrov, D., Köiv, K., Harro, J., 2009. Effect of chronic stress on behavior and cerebral oxidative metabolism in rats with high or low positive affect. *Neuroscience* 164, 963–974.
- Mayberg, H.S., 2002. Modulating limbic-cortical circuits in depression: targets of antidepressant treatments. *Semin. Clin. Neuropsychiatry* 7, 255–268.
- Mayberg, H.S., 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimized treatment. *Br. Med. Bull.* 65, 193–207.
- Mayberg, H.S., 2009. Targeted electrode-based modulation of neural circuits for depression. *J. Clin. Invest.* 119, 717–725.
- Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* 156, 675–682.
- McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol. Rev.* 87, 873–904.
- Merali, Z., Du, L., Hrdina, P., Palkovits, M., Faludi, G., Poulter, M.O., Anisman, H., 2004. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. *J. Neurosci.* 24, 1478–1485.
- Mesulam, M.M., 2000. *Principles of Behavioral and Cognitive Neurology*, 2nd ed. Oxford University Press, USA, February 15, 2000.
- Morgane, P.J., Galler, J.R., Mokler, D.J., 2005. A review of systems and networks of the limbic forebrain/limbic midbrain. *Prog. Neurobiol.* 75, 143–160.
- Morgane, P.J., Mokler, D.J., 2006. The limbic brain: continuing resolution. *Neurosci. Biobehav. Rev.* 30, 119–125.
- Muthukumaraswamy, S.D., Edden, R.A., Jones, D.K., Swettenham, J.B., Singh, K.D., 2009. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proc. Natl. Acad. Sci. U.S.A.* 106, 8356–8361.
- Nestler, E.J., Carlezon, W.A.J., 2006. The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry* 59, 1151–1159.
- Nieuwenhuys, R., 1996. The greater limbic system, the emotional motor system and the brain. *Prog. Brain Res.* 107, 551–580.
- Nieuwenhuys, R., Veening, J.G., van Domburg, P., 1988. Core and paracores; some new chemoarchitectural entities in the mammalian neuraxis. *Acta Morphol. Neerl. Scand.* 26, 131–163.
- Nieuwenhuys, R., Voogd, J., Van Huijzen, C., 2007. *The Human Central Nervous System: A Synopsis and Atlas*, 4th ed. Springer, Berlin, Heidelberg.
- 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., Heinzel, A., Bermpohl, F., Niese, R., Pfennig, A., Pascual-Leone, A., Schlaug, G., 2004. Reciprocal modulation and attenuation in the prefrontal cortex: an fMRI study on emotional–cognitive interaction. *Hum. Brain Mapp.* 21, 202–212.
- 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., Qin, P., Nakao, T., 2010. Rest–stimulus interaction in the brain: a review. *Trends Neurosci.*
- Northoff, G., Walter, M., Schulte, R.F., Beck, J., Dydak, U., Henning, A., Boeker, H., Grimm, S., Boesiger, P., 2007. GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nat. Neurosci.* 10, 1515–1517.
- Panksepp, J., 1998. *Affective 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.
- Panksepp, J., 2006. Emotional endophenotypes in evolutionary psychiatry. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 30, 774–784.
- Panksepp, J., Harro, J., 2004. The future of neuropeptides in biological psychiatry and emotional psychopharmacology: goals and strategies. In: *Textbook of Biological Psychiatry*. Wiley, Hoboken, NJ, pp. 627–660.
- Panksepp, J., Watt, D.F., in press. Why does depression hurt? Ancestral primary-process separation-distress (PANIC) and diminished brain reward (SEEKING) processes in the genesis of depressive affect. *Psychiatry*.
- Philips, 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.
- Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am. J. Psychiatry* 166, 702–710.
- Poulter, M.O., Du, L., Weaver, I.C., Palkovits, M., Faludi, G., Merali, Z., Szyf, M., Anisman, H., 2008. GABA-A receptor promoter hypermethylation in suicide brain: implications for the involvement of epigenetic processes. *Biol. Psychiatry* 64, 645–652.

- Poulter, M.O., Du, L., Zhurov, V., Palkovits, M., Faludi, G., Merali, Z., Anisman, H., 2010. Altered organization of GABA(A) receptor mRNA expression in the depressed suicide brain. *Front. Mol. Neurosci.* 3, 3.
- Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 35, 192–216.
- 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.
- Raichle, M.E., Mintun, M.A., 2006. Brain work and brain imaging. *Ann. Rev. Neurosci.* 29, 449–476.
- Rajkowska, G., O'Dwyer, G., Teleki, Z., Stockmeier, C.A., Miguel-Hidalgo, J.J., 2007. GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology* 32, 471–482.
- 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.
- 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.
- Salvadore, G., Cornwell, B.R., Sambataro, F., Latov, D., Colon-Rosario, V., Carver, F., Holroyd, T., DiazGranados, N., Machado-Vieira, R., Grillon, C., Drevets, W.C., Zarate Jr., C.A., 2010. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. *Neuropsychopharmacology* 35, 1415–1422.
- Sanacora, G., 2010. Cortical inhibition, gamma-aminobutyric acid, and major depression: there is plenty of smoke but is there fire? *Biol. Psychiatry* 67, 397–398.
- 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.
- Sanacora, G., Mason, G.F., Rothman, D.L., Behar, K.L., Hyder, F., Petroff, O.A., Berman, R.M., Charney, D.S., Krystal, J.H., 1999. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch. Gen. Psychiatry* 56, 1043–1047.
- Savitz, J., Drevets, W.C., 2009a. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci. Biobehav. Rev.* 33, 699–771.
- Savitz, J.B., Drevets, W.C., 2009b. Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience* 164, 300–330.
- Schacter, D.L., Addis, D.R., 2007. The cognitive neuroscience of constructive memory: remembering the past and imagining the future. *Philos. Trans. R. Soc. Lond.* 362, 773–786.
- Schacter, D.L., Addis, D.R., Buckner, R.L., 2008. Episodic simulation of future events: concepts, data, and applications. *Ann. N. Y. Acad. Sci.* 1124, 39–60.
- Schlaepfer, T.E., Cohen, M.X., Frick, C., Kosel, M., Brodessa, D., Axmacher, N., Joe, A.Y., Kreft, M., Lenartz, D., Sturm, V., 2008. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33, 368–377.
- Sequeira, A., Klempan, T., Canetti, L., French-Mullen, J., Benkelfat, C., Rouleau, G.A., Turecki, G., 2007. Patterns of gene expression in the limbic system of suicides with and without major depression. *Mol. Psychiatry* 12, 640–655.
- Sequeira, A., Mamdani, F., Ernst, C., Vawter, M.P., Bunney, W.E., Lebel, V., Rehal, S., Klempan, T., Gratton, A., Benkelfat, C., Rouleau, G.A., Mechawar, N., Turecki, G., 2009. Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* 4, e6585.
- 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.
- Shulman, R.G., Rothman, D.L., Behar, K.L., Hyder, F., 2004. Energetic basis of brain activity: implications for neuroimaging. *Trends Neurosci.* 27, 489–495.
- Shulman, R.G., Rothman, D.L., Hyder, F., 2007. A BOLD search for baseline. *NeuroImage* 36, 277–281.
- 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.
- Steele, J.D., Meyer, M., Ebmeier, K.P., 2004. Neural predictive error signal correlates with depressive illness severity in a game paradigm. *NeuroImage* 23, 269–280.
- Stone, E.A., Lin, Y., Rosengarten, H., Kramer, H.K., Quartermain, D., 2003. Emerging evidence for a central epinephrine-innervated alpha 1-adrenergic system that regulates behavioral activation and is impaired in depression. *Neuropsychopharmacology* 28, 1387–1399.
- Surguladze, S., Brammer, M.J., Keedwell, P., Giampietro, V., Young, A.W., Travis, M.J., Williams, S.C., Phillips, M.L., 2005. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol. Psychiatry* 57, 201–209.
- Surguladze, S.A., Young, A.W., Senior, C., Brebion, G., Travis, M.J., Phillips, M.L., 2004. Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology* 18, 212–218.
- Thase, E., 2005. Bipolar depression: issues in diagnosis and treatment. *Harv. Rev. Psychiatry* 13, 257–271.
- van Eijnsden, P., Hyder, F., Rothman, D.L., Shulman, R.G., 2009. Neurophysiology of functional imaging. *NeuroImage* 45, 1047–1054.
- Walter, M., Henning, A., Grimm, S., Schulte, R.F., Beck, J., Dydak, U., Schnepf, B., Boeker, H., Boesiger, P., Northhoff, 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.
- Watt, D.F., Panksepp, J., 2009. Depression: an evolutionarily conserved mechanism to terminate separation-distress? A review of aminergic, peptidergic, and neural network perspectives. *Neuropsychanalysis* 11, 5–104.
- Wiebking, C., Bauer, A., de Greck, M., Duncan, N.W., Tempelmann, C., Northhoff, G., 2010. Abnormal body perception and neural activity in the insula in depression: an fMRI study of the depressed “material me”. *World J. Biol. Psychiatry* 11, 538–549.
- Wiebking, C., de Greck, M., Duncan, N.W., Heinzel, A., Tempelmann, C., Northhoff, G., 2011. Are emotions associated with activity during rest or interoception? An exploratory fMRI study in healthy subjects. *Neurosci. Lett.*, in press.
- Yao, Z., Wang, L., Lu, Q., Liu, H., Teng, G., 2009. Regional homogeneity in depression and its relationship with separate depressive symptom clusters: a resting-state fMRI study. *J. Affect. Disord.* 115, 430–438.