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Integrative deficits in depression and in negative mood states as a result of fronto-parietal network dysfunctions

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Depression is a disorder characterized not only by persistent negative mood, lack of motivation and a „ruminative" style of thinking, but also by specific deficits in cognitive functioning. These deficits are especially pronounced when integration of information is required. Previous research on linear syllogisms points to a clear pattern of cognitive disturbances present in people suffering from depressive disorders, as well as in people with elevated negative mood. Such disturbances are characterized by deficits in the integration of piecemeal information into coherent mental representations. In this review, I present evidence which suggests that the dysfunction of specific brain areas plays a crucial role in creating reasoning and information integration problems among people with depression and with heightened negative mood. As the increasingly prevalent systems neuroscience approach is spreading into the study of mental disorders, it is important to understand how and which brain networks are involved in creating certain symptoms of depression. Two large brain networks are of particular interest when considering depression: the default mode network (DMN) and the fronto-parietal (executive) network (FNP). The DMN network shows abnormally high activity in the depressed population, whereas FNP circuit activity is diminished. Disturbances within the FNP network seem to be strongly associated with cognitive problems in depression, especially those concerning executive functions. The dysfunctions within the fronto-parietal network are most probably connected to ineffective transmission of information between prefrontal and parietal regions, and also to an imbalance between FNP and DMN circuits. Inefficiency of this crucial circuits functioning may be a more general mechanism leading to problems with flexible cognition and executive functions, and could be the cause of more typical symptoms of depression like persistent rumination.

Key words: depression, information integration, reasoning, fronto-parietal network, default mode network

INTRODUCTION

Mood disorders have an enormous impact on work disability and the social economy (Conti and Burton 1994, Murray and Lopez 1996, Lopez and Murray 1998), making them not only relevant to individuals and families but also to the broader public. Depression is a disorder accompanied by persistent negative mood, intrusive thoughts, low self-confidence, reduced self-esteem, and a lack of energy. On the other hand, there are plenty of deficits in depression, which are purely cognitive in nature. These cognitive deficits are especially apparent within executive functions, which are critical for flexible problem solving, action monitoring, and adaptive behavioral modification (Veiel 1997). When thinking about depressive symptoms in the context of work-related issues or general functioning, cognitive impairments become a more important factor of this illness than others (such as emotional and motivational). Interestingly, people who suffer from subclinical or mild forms of depression (e.g., prolonged sad mood) perform quite normally on some cognitive tasks while showing serious impairments in other tasks, especially those requiring flexible thinking, information integration, or hypotheses testing (see, e.g., Sedek and von Hecker 2004). Subclinical depression often precedes clinical depression, and has many common symptoms with this disorder (Flett et al. 1997). It should be kept in mind that in studies where healthy subjects are divided in subclinically depressed

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(dysphoric) and control groups on the basis of score in questionnaires like Beck Depression Inventory (BDI) it is not a clinical diagnosis. BDI is sensitive to changes in severity of depression (e.g., Reynolds and Coats 1986) as well as could indicate depressive disorder (Carter and Dacey 1996) but there are studies showing that heightened BDI scores are not specific to depression but rather indicate presence of dysphoria or other psychological distress (e.g., Roberts et al. 1991). Although it is characterized by less severe and less specific symptoms, the subclinical forms of depression (symptoms of dysphoria) can also disturb work and everyday life and, what most important here, both populations – depressed and dysphoric – demonstrate problems with on-line information integration.

The aim of this article is to review data on cognitive deficits present in people suffering from clinical and subclinical forms of depression, specifically in the context of noticeable changes in brain structure and functioning of people from this population. I will argue that specific and – more importantly – diagnosable changes in neutral information processing occur in sufferers of both major and minor forms of depression. Furthermore, these changes should be especially visible in the face of difficult, non-routine tasks.

As the systems neuroscience approach (i.e. focusing on neural networks instead of separate regions) is becoming an increasingly prevalent method for the description of brain functioning (Menon 2011), I will use it here in order to better elucidate which brain networks are involved in the creation of integrative reasoning deficits stemming from depression. Depression causes problems with many cognitive and emotion processes over the course of its occurrence. These processes rely on distributed brain regions (i.e. neural networks) which cover multiple areas. Two large brain networks are of particular interest when considering depression: the default mode network (DMN) and the fronto-parietal (executive) network (FNP). The DMN network shows abnormally high activity in the depressed, while FNP circuit activity is diminished.

In the following sections, I will present data showing that specific cognitive impairments visible in depression sufferers, also in its mild or subclinical forms, are mainly caused by inefficient functioning of the fronto-parietal network. It is possible that these impairments, namely the inability to flexibly integrate on-line information, can be explained by taking into account indices of FNP functioning. In the first part of this review I will present evidence for a specific, integrative deficit in the depressed population, and depict the neural correlates of integrative reasoning. Next, I will demonstrate that cognitive deficits in depression, especially the inability to integrate piecemeal information into more coherent structures, are mainly due to inefficient frontal area and fronto-parietal network functioning.

DEPRESSION AND REASONING PROCESSES – THE VITAL ROLE OF INFORMATION INTEGRATION DEFICITS

Psychologist explain cognitive deficits in depression by referring to different mechanisms (details in Table I), such as cognitive resources or memory limitations (Hasher and Zacks 1979, Weingartner et al. 1981, Burt et al. 1995), lowered efficiency of cognitive strategies (Hartlage et al. 1993, Kofta and Sedek 1998), and lack of cognitive initiative (Hertel 1997).

One very influential model proposed by Susan Nolen-Hoeksema and Sonya Lyubomirsky places emphasis on the persistent, negative ruminative thinking style present in depression (Nolen-Hoeksema 1991, Lyubomirsky and Nolen-Hoeksema 1995, Nolen-Hoeksema et al. 2008). These ruminations not only occupy ones cognitive resources but, as it has been demonstrated, also impair problem-solving skills. According to the authors of this model, ruminations visible in people suffering from depressive disorders appear to interfere with one or more stages of the problem-solving process: either in the ability to properly define the problem, or in the generation and selection of alternative solutions or implementation of available solutions (Lyubomirsky and Tkach 2004). In a study on hypothetical problem solving, dysphoric students who were allowed to ruminate generated less effective solutions when compared to those who were distracted and to nondysphoric students (Lyubomirsky et al. 1999). There are studies which demonstrate that the construction of novel hypotheses or stimulus representations are at the heart of cognitive impairment in the depressed. For example, Paula Hertel and her collaborators (Hertel and Hardin 1990, Hertel 1997) found that depressed participants failed to initiate new strategies when faced with a novel task, but performed equally as a control group when the task overtly indicated the proper strategy.

Table I

The most popular psychological explanations of cognitive deficits observed in depressed individuals

Theory	Postulated mechanism	References
Resource depletion	Cognitive deficits due to a reduction of cognitive capacity caused by biological (e.g., low level of specific neurotransmitters) or stress-related factors. Impairments in cognitive task performance should be related to the cognitive complexity of problems – the more complex problem the worse performance in depressed group.	Burt et al. 1995, Silberman and Weingartner 1986, Hartlage et al. 1993
Impaired resource allocation	Attentional resources primarily allocated to depression-relevant thoughts (depressive rumination) or task-irrelevant processes (irrelevant features of the task). Similarly to resource depletion theory, impairments in cognitive task performance should be related to the cognitive complexity of problems – more resources needed more deficits observed in depressed population.	Hasher and Zacks 1979, Ellis and Ashbrook 1988, Lyubomirsky and Tkach 2004
Lack of cognitive initiative	Reduced initiation of proper strategies implementation – especially those complex and requiring several steps – as a central deficit in depression. Crucial for depressive impairments revelation task structure: more probable difficulties with task execution in depression when dealing with unstructured task or without explicitly told instruction, and necessity to spontaneous use of complex strategies.	Hertel 1997, Hertel 2004
Cognitive exhaustion	It is an information processing approach assuming that people are likely to engage in systematic mental activity when dealing with problem solving situations. Prolonged cognitive effort without "cognitive gain" (which is postulated to be a cause of depression) results in an altered psychological state-cognitive exhaustion. The essential quality of this transitory state is a generalized impairment of constructive and integrative mental processing.	Kofta and Sedek 1998, von Hecker and Sedek 1999

People suffering from depression as well as from elevated depressive symptoms measured by BDI exhibit difficulties in solving complex cognitive problems such as tasks requiring the rearrangement or maintaining of information and tasks that require reasoning about relations between elements (for review see von Hecker et al. 2013). These deficits become especially evident in tasks requiring the on-line integration of piecemeal information into coherent mental representations. This ability can be formally described as the process of mental model construction (Johnson-Laird 1996). The first stage of this process is learning about piecemeal information that is relevant to a given context. Then, each piece of information which comes in is integrated into the currently constructed mental model in an on-line fashion. Such a mental representation of the world allows for a comprehensive representation of the total set of relevant information, with respect to its meaning and general significance. When properly constructed, mental models facilitate reasoning. However, as their construction is an ongoing and malleable cognitive process, it is prone to perturbation.

In one study testing the mental model construction process in subclinically depressed students (selected from general population on the basis of their Beck Depression Inventory score), Sedek and von Hecker

(2004) used a linear order reasoning task which is ideally suited to probing this process. The linear order reasoning paradigm requires active rearranging of incoming piecemeal information into a comprehensive mental model (mental array). For example, upon learning the series of pairwise information pieces „A is taller than B", „B is taller than C", and „C is taller than D", participants usually rearranged these pieces of information into a coherent mental array spontaneously, without any external cues. We can probe memory functioning as well as on-line information integration ability within the same task just by asking different types of questions. Memory functioning is probed by questions about so called adjacent or one-step pairs within the mental model. In the abovementioned example, relations between A-B, B-C, and C-D elements are one-step pairs. To examine generative processes–specifically the ability to integrate information–questions about so called two-step and end-point pairs are asked. In the abovementioned example two-step pairs are relations between elements A-C and B-D, while the end-point pair is between A-D elements.

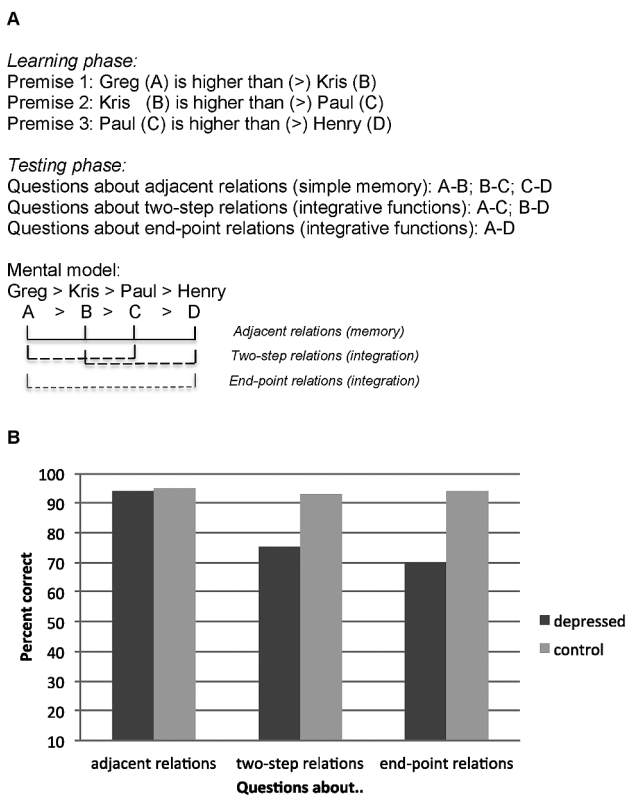

Fig. 1. Schematic representation of linear order paradigm and typical results from studies on depressed and non-depressed participants solving this paradigm. (A) In the learning phase of the linear order paradigm, three premises are presented one at a time (the easiest task is depicted in the example) which can be integrated at the time of learning into a mental model. In the testing phase, questions about previously seen information (adjacent relations) as well as "to be inferred" (two-step and end-points relations) information are asked. (B) A typical pattern of results obtained in several studies examining linear order paradigm performance in a depressed population or in population suffering from negative mood. Depressed and non-depressed differ mostly when integration of information is required.

The robust distance effect, which is observed in healthy populations when solving this kind of task, has been pointed out as evidence for the occurrence of generative processes during the encoding phase of task performance (see Leth-Steensen and Marley 2000). The distance effect means quicker and more precise verification responses for the A-D type of query than for queries such as A-C. It is treated as an indicator of spontaneously generated, constructive mental activity. This activity leads to an integrated memory representation, which gives ready access to implications that go beyond the initially presented information (e.g. information about relation between A-D or A-C elements; for graphical representation see Fig. 1A).

Healthy, non-depressed people have very similar levels of accuracy for inferred and previously presented pairs (Leth-Steensen and Marley 2000). Depressed participants, however, show a decline in accuracy as a function of the number of inferential steps that must be taken. They are as good as control participants when asked about information presented in the learning phase (adjacent pairs), but show significant decline when asked about "to be inferred" (two-step and end-point pairs) information (see Sedek and von Hecker 2004, Sedek et al. 2010, and Fig. 1B).

Employment of different strategies in the first stage of the task (when it is possible to construct a mental model of relations between presented elements) by non-depressed and dysphoric people is the probable cause of observed differences in linear order paradigm completion between those groups. Healthy participants spontaneously rearrange the presented pairs of information into a coherent mental array (A > B > C > D, ">" = "taller") during the material acquisition phase. Depressed participants experience more difficulty with generative reasoning and on-line integration of presented information, and end up with unstructured

material. While learning pairs of elements they would probably be less effective in constructing an integrated mental model, instead memorizing the individual pairs and generating their response only when queried. Results from several studies show that depressed young students remember premises as well as non-depressed participants, but do not spontaneously integrate them (Sedek and von Hecker 2004, Sedek et al. 2010).

A series of studies using the linear order paradigm as well as other paradigms (construction of so called social cliques or situation models in text comprehension, for review see Sedek et al. 2010, von Hecker et al. 2013) have also convincingly shown that cognitive deficits in depression concern primarily the process of piecemeal information integration into coherent mental representations, and not the simple maintaining of information.

In this article I want to focus on the phenomenon of cognitive deficits in depressed people from a slightly different perspective, namely taking into consideration the neural underpinnings of the reasoning processes as well as evidence for neural abnormalities in depression. I want to show that a key factor in the development of reasoning and information integration problems in people with depression is a dysfunction of the fronto-parietal network, which leads to ineffective manipulation of information and a more general deterioration of the working memory mechanism.

BIOLOGICAL UNDERPINNINGS OF REASONING AND INTEGRATIVE PROCESSES

The neuronal underpinnings of the linear order paradigm were explored in two subsequent studies. The first study employed fMRI techniques to investigate two versions of the linear syllogism task: easy (elements in every premise were linked, providing an ideal opportunity for on-line integration) and difficult (elements in the first two premises were unrelated and information in the third premise was a link between them, thus delaying information integration and limiting its occurrence to the third premise presentation) (Brzezicka et al. 2011a). The results showed that delaying the moment of information integration demanded recruitment of the right prefrontal cortex and bilateral parietal cortex, while completion of the task in which integration of information was possible immediately after each premise presentation was based mainly on activation within parietal structures. It seems that parietal cortex activity plays the most important role in the process of information integration. In our study, parietal enhancement was observed during both syllogistic tasks, leading to the conclusion that a mental process present in both types of tasks caused this activity. The most probable candidate for this process, as we proposed, is online integration of incoming piecemeal information (Brzezicka et al. 2011a).

In the second study, EEG techniques were used to explore the psychophysiological correlates of the same linear order paradigm task performance (Brzezicka et al. 2011b). Our results were in accord with the fMRI experiment, indicating medial parietal and anterior prefrontal cortex involvement in information integration during linear syllogisms. As we were specifically interested in answering the question of whether certain frequency bands are specifically related to this type of cognition, we studied EEG transmission patterns determined in the theta, alpha, and gamma bands by means of the Directed Transfer Function (DTF). DTF is an effective method for identifying the organization of neural networks, revealing their short-range and long-range properties. The results of our study showed stronger transmissions in theta and alpha bands from frontal to parietal regions and also within frontal regions when comparing trials requiring information integration to those without such requirements. These results again suggest that fronto-parietal network activity is crucial for the integration of piecemeal information.

Fangmeier and colleagues (2006) conducted a study using a similar version of linear syllogisms, but with three elements instead of four. Their results were analogous to ours, once again indicating prefrontal and parietal engagement in this type of task. Several other studies using transitive inference tasks have also shown that solving this kind of task is associated with bilateral prefrontal cortex and parietal cortex activation (Acuna et al. 2002, Kroger et al. 2002, Hinton et al. 2010). It seems plausible to conclude that the prefrontal cortex is engaged mostly in manipulating and coordinating material, while parietal regions show increased activity when order rearrangement and binding of information is required (see also meta-analysis by Wager and Smith 2003).

As demonstrated by the above selective review of literature on the neural bases of information inte-

gration, there are strong connections between intact prefrontal regions (especially dorsolateral parts) and performance on cognitive tasks requiring online integration of information. It is also very well documented that there are important functional and anatomical divisions within the prefrontal cortex (PFC), and that this huge region of the brain is heterogeneous in nature (e.g., Fuster 2008). The PFC is not only highly involved in higher order cognitive functions but is also implicated in the processing of emotion, and it is the first brain structure which comes to mind when considering the interplay between emotion and cognition. In the next part of this article I will present data from studies aimed at establishing the neural correlates of depression in its major and milder forms, with a special emphasis on prefrontal and parietal regions. Although depression-related disruptions in brain circuit activity are mainly studied using tasks which involve emotion processing, here I would like to focus on non-emotion material processing and therefore on more "cognitive" brain areas in the context of their interconnections with regions involved in emotion processing.

EVIDENCE FOR PREFRONTAL AND PARIETAL ABNORMALITIES IN DEPRESSION

Prefrontal abnormalities

When reviewing works on neuroimaging of cortical dysfunctions in depression, the most frequent result is an overwhelming number of studies demonstrating changes in prefrontal cortex functioning. This abnormal activity of prefrontal regions has been reported in many studies on depressed participants (e.g., Bench et al. 1993, Davidson 1994). There are two distinct lines of results concerning prefrontal abnormalities in depression: increased (mainly in ventral and medial parts of PFC) and decreased (mainly in dorsal and lateral parts of PFC) activity of prefrontal regions (see Table I). This trend is probably due to the different roles that those regions play in behavior regulation, as many studies have shown distinct patterns of brain-behavior relationships for each structure. It is now widely accepted that dorsal and lateral parts of the PFC (DLPFC) are associated with more "cognitive" aspects of behavior, while ventral and medial (VMPFC) parts are mostly connected to "emotional" aspects of information processing (Koenigs and Grafman 2009). It is also worth mentioning that medial and dorsal regions of the PFC are part of distinct, bigger brain circuits – namely the fronto-parietal or executive network (dorsal parts of PFC) and the default mode network (medial parts of PFC). Functional imaging studies convincingly indicate that depression is associated with opposite patterns of activity in ventromedial and dorsolateral parts of the PFC. Of particular importance is the fact that ventral parts of the PFC are usually hyperactive when measured in depressed participants in a rest condition, but exhibit decreased activity during remission of the illness. Conversely, dorsal and lateral PFC regions are hypoactive in depressed populations and increase activity when symptoms remit (Hugdahl et al. 2007). This asymmetrical pattern of PFC activity with increased activity of "emotional" and decreased activity of "cognitive" regions is only one of many lines of evidence for abnormal PFC functioning in depression. Other research areas which deliver evidence for abnormal PFC functioning in depression include studies applying brain stimulation to depressed people, *post-mortem* brain examinations, and observations of depressive symptoms in patient with brain lesions located in the PFC.

Results from brain stimulation studies employing transcranial magnetic stimulation (TMS) and electrical deep brain stimulation (DBS) targeting the dorsal and medial parts of PFC confirm that they play distinct roles in pathophysiology and symptoms maintenance in depression (Koenigs and Grafman 2009). *Post-mortem* studies are able to characterize the cellular and neurochemical substrates of depression, and reveal that depressive disorders are accompanied by alterations in the density and size of neuronal and glial cells in frontal and limbic regions of the brain (Rajkowska 2003). Taken together, the results from all lines of research provide convergent and compelling evidence that the PFC and especially its dorsal parts plays a critical role in producing the cognitive deficits seen in depressive populations. It is important to note that this decreased activity in prefrontal areas occurs in the very same regions which were reported to have higher activation during reasoning (linear syllogisms) and working memory tasks performance: the dorsolateral and anterior parts of the PFC (e.g., Veer et al. 2010).

Parietal abnormalities

The prefrontal cortex is not the only brain region showing decreased activity in depression, and is often accompanied by diminished parietal cortex activity. In a study using positron emission tomography (PET), decreased glucose metabolism was observed in the frontal and parietal cortex of patients suffering from unipolar depression (Biver et al. 1994). Another study using functional magnetic resonance imaging (fMRI) Vasic and coauthors (2009) showed abnormalities within the DLPFC-parietal network in participants with major depression (compared to controls) during working memory task completion. Specifically, they showed a decreased functional connectivity between inferior parietal and superior prefrontal and frontopolar regions in depressed patients when compared to control subjects.

In a recent study using fMRI, Hinton and colleagues (described in von Hecker et al. 2013) examined the brains of subclinically depressed (having above 10 points in Beck Depression Inventory) and control individuals carrying out linear order syllogisms. Unlike in Sedek and von Hecker (2004), both groups performed equally well in this task. However, mildly depressed individuals exhibited a significantly different pattern of brain activation than the non-depressed, having higher levels of activation in parts of the parietal cortex when responding to test queries immediately after their premises had been learned. It seems that subclinically depressed individuals have to activate parietal regions more than the non-depressed in order to achieve the same level of behavioral output.

Prefrontal asymmetry in depression

Some research indicates that prefrontal abnormalities seen in depression are due to disruption of the normal pattern of cerebral laterality (Silberman and Weingartner 1986, Davidson 2004). In fact, epileptics with left-sided epileptogenic lesions suffer from significantly higher levels of depression and anxiety than those with right-sided lesions (e.g., Perini and Mendius 1984). An opposite pattern has been found in patients with brain injury, delivering further evidence for the claim that there is an asymmetry in brain correlates of emotion.

The approach-withdrawal hemispheric laterality model of emotion posits that different emotions are regulated by specific patterns of neurophysiologic activity, and that greater activity in the left frontotemporal areas occurs with positive stimuli. This in turn gives rise to approach-related emotions, while homologous right cortical areas are activated by negative stimuli resulting in withdrawal-related emotions (Davidson 1998, Thibodeau et al. 2006). In this line of research PFC activity is usually measured by extracting alpha band power (8–12 HZ) from EEG signal recorded over left and right frontal and/or temporal regions. As alpha activity is inversely related to cortical activity (Oakes et al. 2004), regions characterized with a relatively low alpha band power recorded from electrodes placed over a particular hemisphere (compared to the other) are treated as exhibiting relatively higher neural activity within the given area.

The results of many electroencephalographic (EEG) studies confirm that depression and sad mood are associated with a disruption of the normal pattern of cerebral laterality, especially within frontal regions. In fact, people with depression demonstrate relatively more right- than left-sided frontal cortex activity as compared to control participants (Allen et al. 2004, Kemp et al. 2010). Davidson suggests that frontal alpha asymmetry may reflect not only the activity of emotional or motivational "brain centers" (i.e. VMPFC), but the activity of the DLPFC as well (Davidson 2004). For example, Cicek and Nalcaci (2001) showed that better performance on the Wisconsin Card Sorting Task is accompanied by relatively lower left frontal alpha power (greater left than right frontal activity). It is highly likely that changes within the alpha-asymmetry reflect not only motivational aspects of behavior but also the course of cognitive processes *per se*.

To test the hypothesis that frontal asymmetry measured by relative alpha power can be a good predictor of performance on linear order paradigm tasks by depressed participants, we conducted a study with mildly depressed (diagnosed from a mild depressive disorder or dysthymia) and control groups (von Hecker et al. 2013). We noticed that in the control group, regardless of the alpha asymmetry index value, the proportion of correct answers was at a uniformly high level across all types of questions. In the depressed group, however, only the group with left-sided frontal brain activity (right-sided alpha asymmetry) did not experience cognitive problems. Thus, only depressed participants with relatively more right-sided frontal brain activity replicated the pattern of results obtained

in previous studies, indicating specific cognitive limitations in the ability to integrate on-line information (Sedek and von Hecker 2004). This pattern may be interpreted in terms of motivational factors; if we assume, according to the classic view on the role of frontal alpha asymmetry, that more right-sided brain activity reflects a greater amount of avoidance, then people who are characterized by such a pattern of frontal activity may also show less engagement in task completion. Under this interpretation, and in line with lack-of-initiative (Hertel 1997) and cognitive exhaustion (Kofta and Sedek 1989) models, a lack of motivation could be seen as an avoidance of the employment of suitable or maximally effective cognitive strategies.

On the other hand, the alpha asymmetry might reflect not only motivational but also cognitive processes *per se*. Davidson (2004) pointed out that the distinction between cognition and emotions is artificial, and that those two phenomena are closely related on the behavioral as well as neural level, especially when it comes to the engagement of prefrontal regions. This perspective may be applied to the neural underpinnings of reasoning and depression as well. As I showed earlier, there is a large overlap in the activity patterns of regions essentially involved in the solving of reasoning tasks and regions that usually show altered activity in depressive states (the fronto-parietal network). Taking this into consideration, one may argue that relatively greater left-sided frontal activity reflects better functioning of the whole fronto-parietal network, and thus may serve as a protective factor from cognitive decline even in the presence of other depression-related factors.

Fronto-parietal network dysfunctions in depression

The supporting evidence for this view comes from studies with rTMS stimulation applied to the PFC and parietal cortex in depressed participants. George and coworkers (1997) found that applying fast (inducing cortical excitation) rTMS over the left PFC has an antidepressant effect. He interpreted it as a result of normalization of left PFC hypometabolism. Rosenberg and others (2002) showed comparable antidepressant efficacy after both slow and fast rTMS over the left the PFC, which seems paradoxical in terms of the 'normalization of left PFC hypometabolism' claim; slow rTMS should further decrease left PFC metabolism (see, e.g., Wassermann and Lisanby 2001). The latter result can be interpreted in terms of the strengthening of functional connectivity in this fronto-parietal depression circuit by both slow and fast rTMS (Schutter et al. 2003). Even more interesting, and in agreement with the view of prefrontal and parietal regions cooperation as being crucial in depression, are the results of a study by Van Honk and coworkers (2003). They demonstrated reductions in many indices of depression in healthy volunteers after slow rTMS over the right parietal cortex.

Our own preliminary data using the DTF method on resting EEG in mildly depressed (diagnosed from a mild depressive disorder or dysthymia) and control participants confirms such thinking (unpublished data). Comparison of the propagation patterns in main frequency bands in both groups indicated a lack of significant casual sources in depressive patients, which were well localized in controls. These results support and extend the notion of disturbances in cortico-cortical fronto-parietal network functioning in depressed participants, and are in accordance with the observation of reduced activity in frontal and parietal regions (Thomas and Elliott 2009) in depression or after rTMS administration (Schutter 2009), as well as with studies on testosterone treatment (Schutter et al. 2005) effects in people suffering from major depression.

In summation, brain imaging studies in depression have documented abnormalities in regions involved in affective as well as cognitive behavior, such as the anterior cingulate cortex and the orbitofrontal cortex, as well as in fronto-parietal networks. This latter neural net activity is related to attention or executive functions and, as I showed earlier in the text, integrative functions. Furthermore, people suffering from depression may recruit greater prefrontal or parietal activity in order to achieve similar task performance to control subjects. More recent theories go far beyond simply pointing to ''dysfunction in the left hemisphere'' or ''hypoactivity in the frontal lobes'', and attempt to elucidate a more integrated picture of the neural mechanism underlying depression (Jacobs 2004). Schutter and coauthors (2003) suggest that a cortical circuit involving left frontal and right parietal regions is important in depression, and that decreased functional connectivity between these regions occurs in depression.

DEFAULT MODE NETWORK DISTURBANCES IN DEPRESSION

The default mode network (DMN) is a set of brain regions, located mostly medially, which shows heightened and coherent activity during rest. The medial prefrontal cortex, rostral parts of the anterior cingulate cortex, precuneus, posterior cingulate cortex, and retrosplenial cortex are considered to be core areas forming the DMN (Raichle 2010). Besides increased activity during rest periods, the DMN exhibits reduced activity during cognitive tasks. What is especially important in the context of this article is the lack of DMN suppression during cognitive activity reported in depression (Sheline et al. 2009), which is thought to be the reflection of enhanced ruminative processes taking place in people suffering from depression. This failure to suppress the DMN, especially its medial prefrontal parts, is interpreted as a manifestation of focusing on negative thoughts rather than a reflection of inability to engage executive processes (Menon 2011).

Marchetti and colleagues (2012) proposed that depressive disorder is characterized by an imbalance in activity of two DMN components – task positive (TP) and task negative (TN) – resulting in an overpowering of TP by TN activity. The TN-TP imbalance is thought to be associated with a dysfunctional focusing on internal stimuli, which can result in difficulties in diminishing TN activity during transition from a resting state to a cognitive task. Similarly, Price and Drevets (2012) see DMN abnormalities as the main brain dysfunction in depression responsible for causing most depressive-like symptoms. What I wish to emphasize here is that DMN disturbances in depression do not show a direct link to disturbances in integrative processes. It is more likely that the prefronto-parietal network abnormalities are a direct cause of information integration problems, problem solving difficulties, and working memory/executive functions dysfunction in depression. As brain networks are heavily interrelated, it is also highly possible that these two circuits influence each other and that DMN disturbances cause frontal and parietal activity changes or, at least, that these two circuits influence each other.

A study by Jack and coauthors (2012) supports such thinking. They proposed that attention-demanding cognitive tasks activate the task-positive (i.e. executive or fronto-parietal) network and simultaneously deactivate the default mode network, resulting in an anti-correlation between these networks in the resting state. They showed that these reciprocally inhibitory effects reflect two separate cognitive modes, each of which activates one set of regions and suppresses activity in the other. They argue that the DMN is associated with social information processing (reasoning about self-related things and the minds of others), whereas the executive attention network or fronto-parietal network is associated with non-social information processing, especially in reasoning about physical objects.

This is especially important for understanding neural abnormalities in depression. Zhou and others (2010) showed an increased anti-correlation between DMN and the executive network in depression. These findings could explain more than just biased processing of negative and self-relevant information in depression. It is a possible explanation for inferior reasoning and information integration in this group, which could be the result of an inhibitory influence of DMN on the executive network. Another study by Zhang and colleagues (2011) similarly showed that in depression the DMN leads organization of the whole brain during rest, resulting in a perturbation of other neural networks. Additionally, the triple network model (Menon 2011) predicts that dysfunction in one core network can impact other networks. Figure 2 depicts a possible mechanism, including DMN and FPN interactions, which leads to problems with information integration in depression.

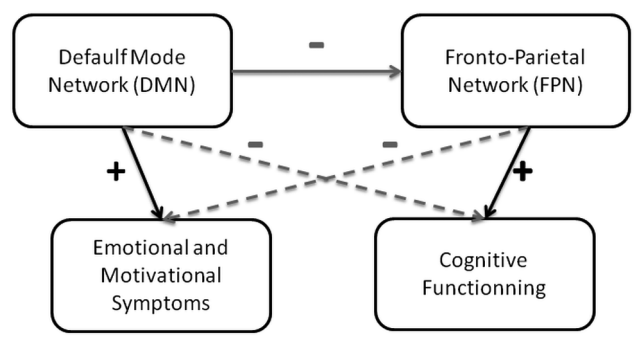

Fig. 2. The hypothetical mechanism of interplay between DMN and FPN circuits leading to cognitive disturbances in depression. DMN hyperactivity could cause problems with executive functions in depressed populations by suppressing FNP functioning indirectly. These problems include difficulties in information integration. However, the direct source of cognitive problems is hypoactivation of the FPN.

CONCLUSIONS

Network models are now increasingly being used to study brain organization in general, and also to study brain and cognitive disturbances in psychopathology. Analyses of large-scale networks have shown them to be powerful tools for investigating the core features of many mental disorders (see Menon 2011), and also seem to be useful in studying depression. In this article I presented the hypothesis that the cognitive deficit characteristics exhibited by people suffering from depression are caused by an inefficient functioning of brain circuits, and especially one specific cortical circuit: the fronto-parietal network. As I showed earlier, depression is often related to dysfunction of so called "executive" functions. Evidence from many studies using the linear order paradigm shows that those deficits are especially visible when we ask depressed people to integrate piecemeal information, and are not observable in measures of more basic memory functions (Sedek and von Hecker 2004; von Hecker et al. 2013). Importantly, this pattern is consistently replicated on dysphoric as well as depressed patients. This "ability to integrate information" seems to be a core mechanism of reasoning and working memory. Both reasoning and working memory functioning relies on efficient prefrontal and parietal cortex functioning, and especially on fronto-parietal network interactions (Brzezicka et al. 2011b).

As I have described in earlier sections of this article, depression is related not only to subcortical abnormalities but also to very specific cortical dysfunctions. This is in accordance with Helen Mayberg's neural model of depression, assuming a ventral-dorsal and crucially also a limbic-cortical opposition in brain activity in depression (Mayberg 1997), with limbic structures being more activated and having a suppressing effect on the DLPFC. Although most studies on depressed participants indicate worse performance on cognitive tasks accompanied by lower DLPFC activity, some exceptions exist. Data from several studies demonstrates that depressed people exhibit greater DLPFC activity during tests involving executive functions compared to non-depressed populations, while simultaneously maintaining a task performance level comparable to the control group (Harvey et al. 2005, Wagner et al. 2006). This greater cortical activity may be a neural manifestation of the greater effort required to maintain normal performance, and is still in accord with the hypothesis of prefronto-parietal circuit disruption as a source of cognitive problems in depression. In order to prove the hypothesis of disruptive PFC-parietal network as a cause of integrative problems observed in depression, a mediation analysis should be performed on data collected simultaneously for linear syllogisms and PFC-parietal cortex interplay. Inefficiency of the fronto-parietal circuit resulting in lower cognitive control may be a more general mechanism which leads to problems with flexible cognition and executive functions, and could be the cause of more typical symptoms of depression like persistent rumination which are very often present in depressive disorders (Siegle and Thayer 2003).

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