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The Default Mode Network and Recurrent Depression:

A Neurobiological Model of Cognitive Risk Factors

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Abstract

A neurobiological account of cognitive vulnerability for recurrent depression is presented based on recent developments of resting state neural networks. We propose that alterations in the interplay between task positive (TP) and task negative (TN) elements of the Default Mode Network (DMN) act as a neurobiological risk factor for recurrent depression mediated by cognitive mechanisms. In the framework, depression is characterized by an imbalance between TN-TP components leading to an overpowering of TP by TN activity. The TN-TP imbalance is associated with a dysfunctional internally-focused cognitive style as well as a failure to attenuate TN activity in the transition from rest to task. Thus we propose the TN-TP imbalance as overarching neural mechanism involved in crucial cognitive risk factors for recurrent depression, namely rumination, impaired attentional control, and cognitive reactivity. During remission the TN-TP imbalance persists predisposing to vulnerability of recurrent depression. Empirical data to support this model is reviewed. Finally, we specify how this framework can guide future research efforts.

Keywords: depression, default mode network, vulnerability, rumination, attention, cognitive reactivity

1. Introduction

Depression is a severe psychiatric illness that is associated with high levels of personal suffering and with substantial costs to society (Gustavsson et al., 2011). Major depression has a life-time prevalence of 15-30% (Kessler et al., 2003). Pharmacological and psychological interventions show efficacy in the short term. However, there is a pressing need for improved long term effectiveness of treatments. This is especially true with regard to the prevention of *recurrence*. Numerous studies indicate that remitted patients have a 70% risk of developing new depressive episodes. Moreover, the risk of new episodes increases as a function of the number of previous episodes (Keller, 2003). After multiple prior episodes of depression even minor stressors can become triggers for new depressive episodes (Monroe and Harkness, 2005).

Understanding risk for recurrent depression in remitted patients is important for the development of its effective treatment. The neural correlates of depression are increasingly well understood (for reviews, see Davidson et al., 2002; Disner et al., 2011; Price and Drevets, 2012). For instance, imaging research has identified the neural circuitry involved in emotion-attention interactions as an important focus in the pathophysiology of depression. This has led to a conceptualization of depression as a failure to recruit top-down control (related to prefrontal regions – e.g., dorsolateral prefrontal cortex, DLPFC) to regulate limbic activity (e.g., amygdala; Davidson et al., 2002; Mayberg, 1997; Ochsner et al., 2002; Phillips et al. 2003; Phan et al., 2004). A crucial structure in this circuitry is the anterior cingulate cortex (ACC) with the ventral ACC processing of emotion-related signals, and the dorsal ACC involved in response selection and conflict monitoring signals (Bush et al., 2000). ACC signals to DLPFC to alter the direction of attention or to modify the distribution of processing resources (Hopfinger et al., 2000). This can inhibit emotion processing in amygdala via connections with other frontal regions, such as orbitofrontal cortex (OFC; Taylor and Fragopanagos, 2005).

Depression-related disruptions in this circuitry are well established especially during tasks involving emotion processing. These neural disruptions correspond to specific information-processing characteristics observed in depression (Disner et al., 2011; De Raedt and Koster, 2010). Depressed individuals are unable to swiftly reallocate attention away from negative to positive or task-relevant information (Koster et al., 2005; Leyman et al, 2007). Depression-related failures to exercise cognitive control in the face of stressful information appear to enhance the tendency towards rumination (Koster et al., 2011). A recent fMRI study found that difficulty disengaging attention from negative information is related to depressive brooding, and that brooding was correlated with DLPFC activity (Vanderhasselt et al., 2011). Moreover, ACC related cognitive impairments were found to increase linearly with the number of prior depressive episodes illustrating that such effects persist even after remission of depression (Vanderhasselt and De Raedt, 2009). Thus, deficient cognitive control is considered an important vulnerability factor for recurrent depressive episodes (for a review, see De Raedt and Koster, 2010), a view supported by recent findings that such deficits predicts recurrence of symptoms in a sample of patients in remission (Demeyer, De Lissnyder, Koster, and De Raedt, 2012).

Alongside this focus on the "task-related" disruption on fronto-limbic circuits there is a growing interest in disruptions in "task-independent" resting state neural networks in the pathophysiology of depression (Hamilton, Furman, and Gotlib, 2011). In the current article we develop a framework of *Default Mode Network* (DMN) dysregulation as a neural substrate of depression. Central to our model is the notion that DMN is a system comprised of two tightly locked but anti-correlated subcomponents namely the *Task Negative* (TN) and *Task Positive* (TP) circuits (Fox et al., 2005). DMN dysregulation has been implicated in a range of psychiatric disorders (Broyd et al., 2009), such as, for instance, depression and schizophrenia (e.g. Bar, 2009b; Northoff and Qin, 2011; Northoff et al., 2011; Pizzagalli, 2011; Whitfield-Gabrieli and Ford, 2012). Our hypothesis is that dysfunction in the TP and TN components can result in an imbalance in the default mode system as a whole leading to deficits in the psychological functions

subserved by the DMN. These aberrant psychological functions are thus thought to embody cognitive deficits that have been specifically linked to depression such as rumination and poor attentional control. In particular, we argue that DMN dysregulation, mediated by key aspects of depression-related cognitive impairment, underpins neurobiological risk for *recurrent depression* (Figure 1). Specifically, we propose that an imbalance between TP and TN circuits in the DMN system drives the three well-establised components of cognitive vulnerability for recurrent depression: (1) rumination, (2) impaired attentional control, and (3) cognitive reactivity. These risk phenomena have been studied and conceptualized independently of each other in the past, while here we propose DMN system dysregulation as a common underlying mechanism to explain them. The aim of this paper therefore is to explain cognitive and neural processes underpinning risk for recurrent depression in terms of our emerging knowledge of the resting brain. First, we will describe current understanding of the DMN, its neural correlates, and functional significance. Second, the state of art concerning the role of the DMN in major depression will be presented, shedding light on specific neuropsychological features. Third, we will argue that the TN and TP components of the DMN system are core neural hubs underpinning the main cognitive risk factors for recurrent depression. We will describe the available data supporting this proposition. Finally, future directions for research are described, based upon our new framework that allows more specific predictions of the interplay between the TN, the TP and cognitive risk factors to be tested. In this way the current paper builds upon previous views on DMN in depression (Bar, 2009b; Northoff et al., 2011) and recurrent depression (De Raedt and Koster, 2010) to establish an integrative understanding of neural and cognitive risk factors for recurrent depression.

2. The Default Mode Network (DMN) as a system of coordinated "Task-Positive" and "Task-Negative" components

The resting brain exhibits spontaneous patterns of self-organization framed in terms of multiple long range neural networks characterized by task independent patterns of temporally coherent neural activity (Beckmann et al., 2005; Damoiseaux, et al., 2006; De Luca et al., 2006; Raichle et al., 2001; Shulman et al., 1997). Perhaps the most robust regions considered part of this resting network consists of a series of primarily midline regions including the medial prefrontal cortex (MPFC), the most rostral parts of the anterior cingulate cortex (rACC), the precuneus, the posterior cingulate cortex (PCC), and the retrosplenial cortex (Rsp) along with more lateralized regions of the parietal cortex (Raichle and Snyder, 2007) as well as mediolateral temporal cortex (MLTC) and hippocampal formation (Buckner et al., 2008) (Figure 2). This network shows enhanced functional coherence during rest which parametrically attenuates in an event-related fashion during cognitive tasks (McKiernan et al., 2003; Singh and Fawcett, 2008). Originally, characterized as underpinning a default mode of brain activity, the circuitry in this network has been proposed to subserve internal attention (Fox et al., 2005), during which internally-generated information dominates and exogenous stimulation is processed only to a limited extent (Chun et al., 2011). It has also been linked to other psychological functions, characterized by predominant internally-oriented attention. *Mindwandering,* for instance, is defined as naturally occurring mental activity which spontaneously and automatically arises when an individual is not engaged in an attention demanding task (Gruberger et al., 2011). Mason et al. (2007) manipulated proficiency on a working memory task during rehearsal and a novel task. They found a strong positive correlation between degree of mindwandering and BOLD signal changes in the MPFC, PCC, precuneus, superior frontal gyrus, rACC, and middle and superior temporal gyrus (see also Christoff et al., 2009). *Self-related processing* is the evaluation of information in relation to an individual's own mental concept of themselves (Christoff et al., 2011). Studies have found increased activity in the MPFC and PCC during self-related processing tasks compared to rest (Fossati et al., 2003; Gusnard et al., 2001; Mitchell et al., 2006; Ochsner et al., 2005). Interestingly, empirical data show that different self-related sub-processes involve specific brain

components. While the ventromedial prefrontal cortex (VMPFC) plays a role in identifying stimuli as self-salient (Gusnard et al., 2001; Schimtz and Johnson, 2007), the PCC, the lateral parietal cortex, and the hippocampal formation are considered important for the processing of autobiographical and past self-relevant stimuli (Cavanna, 2007). Other neuropsychological functions are also associated with activity within these regions, such as autobiographical memory (Addis et al., 2007), theory of mind, (Mitchell et al., 2005) and future prospection (Andrews-Hanna et al., 2010; Sonuga-Barke and Fairchild, 2012).

Other influential theories have tried to capture the psychological functions of the DMN. The *Internal Mentation Hypothesis* (Buckner et al, 2008) postulates that the sorts of mental activities subserved by this resting network (e.g. MPFC, rACC, the precuneus, PCC, Rsp, LPC MLTC, and hippocampal formation) involve the ability to project oneself somewhere in time (i.e., past or future) or space (i.e., theory of mind). Interestingly, some memory-related brain regions (e.g. MTLC and hippocampus) also play an important role in facilitating mental simulation (Andrews-Hanna et al., 2010). Moreover, MTLC, by binding past-related information and providing building blocks for future scenarios (Hassabis and Maguire, 2007), subserves the ability to project oneself in the future (Andrews-Hanna et al., 2010), while hippocampus and frontoparietal midlines are activated during tasks involving autobiographical memory and future prospection (Andrews-Hanna et al., 2010). Alternatively, Bar et al. (2007) have argued that the regions within this network play a key role in associative conditioning which in turn is crucial as basic "*units of thought*", given their intrinsic nature to connect multiple strands of information. Bar et al. define such associations as multimodal links between perceptual, conceptual, and emotional representations (e.g. schemata) which are formed by a lifetime of extracting repeating patterns and statistical regularities from experience. Several studies (Bar and Aminoff, 2003; Bar, 2004; Aminoff et al., 2007) have shown that attending to highly inter-associated objects activates the medioparietal cortex, MTLC, and MPFC. It is noteworthy that from a theoretical standpoint these associative links rely on memory processes, a fact supported also by the contribution of the

MTLC. Recently, Bar (2009a) suggested that associative conditioning goes beyond the simple stimulus-stimulus link – rather it may also be seen as a "*mindset*" which shapes behavior even at the level of sophisticated psychological functions, such as motivations and expectations. A mindset is indeed regarded as a "*list of needs, goals, desires, predictions, context-sensitive conventions and attitudes*" (Bar, 2009a, pag. 1239), that form a specific set of salient memories, attitudes and predictions interacting with environmental stimuli. Crucially, in this model the response to stimuli (either internal or external) is almost entirely dependent on the specific kind of mindset operating (mindset-stimulus interaction specificity).

Because there is some evidence that internally-oriented attention associated with this circuitry in some ways impairs efficient performance on most tasks requiring substantial controlled processing (Barron et al., 2011; Braboszcz and Delorme, 2011; MacLean et al., 2009; for a review see Smallwood and Schooler, 2006) and because failures to attenuate neural activity in this system have been shown to be linked to attentional lapses (Christoff et al., 2009, Weissman et al., 2006), it has been characterized as a *task negative* (TN) component . Such network is tightly coordinated with a second resting brain network (Cabeza and Nyberg, 2000, Corbetta and Shulman, 2002), which shows similar patterns of low frequency (~0.01 - 0.08 Hz) functional connectivity (Fox et al., 2005). This second component of the default mode resting network consists of regions, such as the DLPFC, the inferior parietal cortex (IPC), the supplementary motor area (SMA), frontal eye fields, and extrastriate cortex (Fox et al., 2005; Fransson, 2006; Figure 2), which are routinely activated during attention demanding, goal-directed task performance (Dosenbach et al., 2006; Duncan and Owen, 2000). For this reason it has been termed the task positive component. During rest the TP has been claimed to subserve intermittent "*external awareness*", defined as the conscious perception through different sensory modalities of one`s surrounding environment (Vanhaudenhuyse et al., 2011).

Crucially, TN and TP activity is thought to be anti-correlated both in rest and task periods (Figure 3). Given such tightly anti-correlated and coordinated patterns of neural activity, and the complementary nature of the associated psychological functions, the TP and TN have been conceptualized as two components of one system regulating activity within the brain's default state (Broyd et al., 2009; Sonuga-Barke and Castellanos, 2007). It has indeed been suggested that normal activity during rest within this system involves the "toggling" between TN and TP activity (Fox et al., 2005; Fransson, 2005, 2006). While the TN and TP show a putative antagonism of function, at the psychological level this TN-TP interplay has been reframed in terms of a coordinated ongoing switching between internally- vs. externally-oriented attention (Fransson, 2005, 2006; Sonuga-Barke and Castellanos, 2007). In a recent study, healthy participants were required to simultaneously rate the intensity of their internally- and externally-oriented attention during rest (Vanhaudenhuyse et al., 2011). Consistent with previous results, internal and external awareness was found to be anti-correlated (Spearman`s rho = -.44), and stronger internal awareness correlated with increased activity in the TN regions, such as MPFC, ACC, PCC, precuneus, and parahippocampal cortices, while external awareness correlated with TP structures, such as the DLPFC and the IPC. Sridharan et al. (2008) identified the right fronto-insular cortex (rFIC), consisting of the right VLPFC and the right insula, as a key region in the control of TP-TN interplay – with activation preceding the switch between TN and TP activity (so called salience network; Seeley et al., 2007). Moreover, a similar analysis revealed that the TN component exerts more influence than the TP in this process (Uddin et al., 2009). In sum, this antithetical relation between TN and TP has been proposed by many to constitute a core element of DMN function (Broyd et al., 2009; Fox et al., 2005; Sonuga-Barke and Castellanos, 2007).

However, the TN-TP anti-correlation is still under debate (Cole at el., 2010; Van Dijk et al., 2010). It has been argued that regressing out the mean global signal, a pre-processing procedure performed to control for unwanted variation in the BOLD signal, may artificially introduce spurious anti-correlations between time series (Murphy et al., 2009). Although previous studies

have not reached a consistent conclusion on this issue (Chang and Glover, 2009; Fox et al., 2009; Weissenbacher et al., 2009), improved analytical approaches have been recently proposed, such as regressing out time-locked cardiac and respiratory artifacts (RETROICOR; Glover et al., 2000) or controlling for non-neuronal sources of noise (CompCor; Behzadi et al., 2007). Adopting these procedures does not extinguish the TN-TP anticorrelation (Chai et al., 2012; Chang and Glover, 2009)

Function-wise, there are a number of hypotheses concerning the purpose of TN-TP switching during rest. One suggestion is that dominant internally-focused attention, supported by the TN connectivity, is interleaved by periodic and intermittent phases of TP increased connectivity, which reflects a general state of vigilance, by which the environment is scanned for novel and unexpected stimuli, to increase preparedness implicated in response selection, and planning of actions (Fransson, 2005, 2006). The possible function of the TP in mitigating the internally-oriented attention is allowing external information to be processed more effectively. This would provide a clear evolutionary advantage in terms of survival and adaptation to the environment, enhancing the likelihood to detect threatening stimuli (Broyd et al., 2009). Alternatively, during rest the TN connectivity may reflect the internal generation of different predictions and mental simulations about external events, both of which are TN-related functions (Bar, 2009a; Bruckner et al., 2008). Therefore, during this ongoing internal mentation, the TP may allow people to constantly update self-relevant information processing, so that individuals can anticipate short and long term outcomes through different predictions and simulations (Sonuga-Barke and Castellanos, 2007).

The balance between TP and TN may be disturbed in a number of ways in both normal and clinical populations. During rest, one DMN component can temporally dominate over the other, leading to an imbalance in related psychological functions. Alternatively, TN and TP may become desynchronized so that these two orientations enter into a competitive rather than a

complementary relationship, or, on the contrary, they may show an excessive anti-correlation, resulting in an aberrant antagonism. There may be a failure to attenuate sufficiently during the transition to task performance in one component compared to another so residual activity within either the TP or the TN interferes with task performance and attention. All of these forms of disruption are likely to have profound implications for mental functioning and personal well-being. Indeed several abnormalities in TN-TP interplay at the level of functional connectivity have been reported to impact on both mental health and behavioral performance.

An exaggerated anti-correlation between the TN and the TP was reported in several severe (psycho)pathologies, such as schizophrenia (Zhou et al., 2007) and depression (Zhou et al., 2010), whereas a reduced and blurred anti-correlation was reported in autism (Kennedy and Courchesne, 2008) and in healthy individuals showing less consistent behavioral performance (Kelly et al., 2008, Hampson, et al., 2010). These data speak in favor of the existence of an optimal degree of anti-correlation between the two networks, above and below which detrimental effects can be observed. Thus, the nature of the antithetical relation between the TN and the TP should be considered when explaining how resting state activity influences mental health and psychopathology.

More recently, a new approach investigating the imbalance between the TN and the TP has been proposed to take into account the temporal perspective, defined as "*dominance*" of one network over the other one (Hamilton et al., 2011). For instance, TN-dominance over the TP is operationalized as the time points where the TN BOLD signal is greater than the TP BOLD signal. The increased duration of TN-dominance over the TP is thought to reflect elevated levels of TN functions. This approach, which has the clear advantage of not needing to take into account the strength of the anti-correlation but only the ongoing temporal pattern of the DMN components, provides a new and promising index. This index might capture individual differences in thinking

styles such a rumination, a crucial factor in depression (Berman and Jonides, 2011; Hamilton et al., 2011).

Finally, rest-to-task transition appears to be important for both the DMN components (Northoff et al., 2010; Northoff et al., 2011) and disrupted attenuation or impaired activation of DMN system activity should be carefully considered to explain cognitive impairment. Previous models have focused on the failure to attenuate spontaneous TN neural processes during active task performance as a cause of attentional lapses and related cognitive deficits (Sonuga-Barke and Castellanos, 2007). A key idea in our model is that DMN abnormalities during rest-to-task transitions relating to both TN and TP can undermine mental and brain activity in a way that has implications for depression-related cognitive risks, so that two aberrant non-mutually exclusive profiles may be proposed (Figure 4). The first relates to a failure to deactivate TN when an individual begins to engage in a goal-oriented task and continues to show an inappropriate level of spontaneous and intrusive internally-oriented TN activation. We term this *TN-persistence*. The second relates to a failure to fully engage TP regions during rest-to-task transition so that the attention to task-relevant stimuli is reduced. This is called *TP-deficiency.* Interestingly, both TN-persistence and TP-deficiency have been reported in mental disorders (Grimm et al., 2009; Hooley et al., 2005; Mitterschiffthaler et al., 2008; Sheline et al., 2009) as well as in some conditions in healthy participants (Polli et al., 2005; Weissman et al., 2006).

Within our framework we propose specific links between DMN aberrations at the level of TN and TP functioning in relation to cognitive risk factors, known to be of crucial importance for recurrent depression. We first turn to research on the DMN in depression.

3. The Default Mode Network (DMN) in depression

Several aspects of DMN system dysregulation have been linked to depression.

3.1 *Altered functional connectivity and temporal sequencing during rest*

Studies have reported a hyper-connectivity of TN brain regions in depression during rest (e.g. Berman et al., 2011, Zhou et al., 2010). Greicius et al. (2007) were the first to report increased functional connectivity of the subgenual cingulate cortex (SubG), the thalamus, the OFC, and the precuneus in depressed individuals. In particular connectivity of the SubG with other TN areas distinguished depressed from healthy participants (Cohen`s $d = 1.01$) and was positively correlated with depression refractoriness, as measured by the length in weeks of the current episode. The SubG was also functionally connected with thalamus during rest, which led the authors to conclude that "[…] *in depressed subjects, activity in medial thalamus is excessively coupled to activity in the 'affective' subgenual cingulate, at the cost of reduced connectivity to the 'cognitive' dorsal anterior cingulate*" (Greicius et al., 2007; pp 435). Consistent with this, non-refractory depression was associated with reduced fronto-limbic connectivity - a finding congruent with reduced inhibitory control (of the PFC) over the limbic system activity seen in depression (Dannlowski et al., 2009). Moreover, refractory depression has been related to diminished thalamo-frontal connectivity (Lui et al., 2011). These results suggest a possible differential role of the thalamus in the various resting state functional connectivity profiles among depression-related subtypes. This latter finding provides an initial justification to consider the specificity of TN activity in recurrent vs. non refractory depression. Note that the findings relating to this are not fully consistent as Bluhm et al., (2009) reported increased connectivity between the PCC/precuneus and caudate nucleus in healthy controls, whereas medication-free depressed individuals did not show enhancement of connectivity in the areas reported by Greicius et al. (2007). These authors suggested that, given the role of the caudate nucleus in reward processing (Yacubian et al., 2006), this connectivity pattern may be related to anhedonia in depression. While these inconsistent results may simply be due to the use of different methods of analysis (Hasler and Northoff, 2011), they could also be linked to different stages of the depressive illness (e.g. strengthened vs. decoupled links between emotion, cognition and bodily sensations), whereby

early (or first onset) and recurrent (or chronically) depressed individuals may show different connectivity patterns. This latter idea is in line with our proposal to investigate the specificity of the DMN components after remission, to focus on "scars" of former episodes. Indeed it has been proposed that neurobiological abnormalities in depression increase with each new episode, thereby increasing individual vulnerability (for a review, see De Raedt and Koster, 2010).

Recently, the specific temporal order of activation in DMN related regions in depression has been investigated using Granger Causality Analysis (Hamilton at al., 2010). Increased activity in the hippocampus predicted subsequent activation of the SubG, which in turn showed a reciprocal augmentation with the MPFC. Additionally, SubG activity seemed to inhibit the dorsal medioprefrontal cortex (DMPFC), the PCC and the DLPFC. Interestingly, increased hippocampal activation also preceded reduced activation of the DLPFC - suggesting that hippocampus hyperactivity may contribute in important ways to resting state abnormalities in depression. Other recent connectivity data also supports the idea that the hippocampus plays an important role in depression. For instance, increased hippocampus functional connectivity with thalamus, frontal and posterior cingulate regions has been reported in an elderly depressed population (Goveas et al., 2011). Therefore, even though the hippocampus was not consistently detected as part of the TN in earlier studies, this area and its functions, such as contextual memory retrieval, are increasingly considered important. This region seems to contribute to TN functional connectivity both in healthy and depressed subjects (Buckner, 2010; Hamilton et al., 2010; Perry et al., 2011).

An important question about aberrant DMN is the extent to which increased functional connectivity could be due to well-known anatomical abnormalities in depression (e.g. Davidson et al., 2002). Although functional and structural connectivity (i.e. Diffusion Tensor Imaging, DTI) can be highly overlapping, nevertheless they do not map onto each other one-to-one in healthy subjects (Greicius et al., 2009). A recent review indeed indicates that strong functional connectivity can be present even among anatomically unrelated structures (Honey et al., 2010).

Unfortunately no studies have investigated this issue in depressed patients thus far, but it has been proposed that the divergence between structural and functional connectivity might be strong in mood disorders, perhaps mediated by neurochemical imbalance (Hasler and Northoff, 2011). This provides an interesting area of research, since functional connectivity research in depression could capture specific pathological features above and beyond existing anatomical models (e.g. Price and Drevets, 2012).

3.2 *DMN rest-to-task transition in depression: TN-persistence vs. TP-deficiency.*

Given the partial overlap between DMN regions and emotion regulation structures (e.g. Goldin et al., 2008; Ochsner et al., 2004), recent studies have investigated how these regions respond to emotional stimuli in depression, and specifically whether rest-to-task transition in emotional contexts is affected by TN-persistence and TP-deficiency (Figure 4).

Several recent studies report failures of depressed individuals to deactivate TN regions during task engagement (Grimm et al., 2009; Sheline et al., 2009). Grimm et al. (2009) reported reduced rest-to-task attenuation of the rACC, VMPFC, and dorsal PCC activity to the presentation of emotional pictures by participants with major depression compared with healthy participants. Amongst the depressed individuals reduced deactivation in VMPFC was highly correlated with feelings of hopelessness, whereas reduced deactivation in the dorsal PCC was correlated with depressive symptoms. In another study, depressed participants failed to show a reduction of BOLD signal in the rACC, VMPFC, lateral temporal cortex (LTC), and lateral parietal cortex (LPC) during both passive viewing and active reappraisal of emotional stimuli (Sheline et al., 2009). Depressed individuals also displayed greater activation in response to negative compared with neutral pictures in left parahippocampus, right hippocampus, and left amygdala during a passive viewing task suggesting that both automatic and effortful processing of emotional stimuli is influenced by aberrant TN-persistence.

Important for our framework, currently depressed patients show TP-deficiency during rest-to-affective task transition, underlining that not only is TN less effectively suppressed, but also that TP brain regions are less efficiently activated in depression. Despite a lack of activation studies which take into account the whole TP network, several studies report that a key TP region, that is the DLPFC, shows deficient activation patterns during rest-to-affective task transitions (Fales et al., 2008, 2009; Holmes and Pizzagalli, 2008; Mitterschiffthaler et al., 2008; Siegle et al., 2007). Depressed individuals exhibited less recruitment of the DPLFC compared with healthy individuals in a modified emotional Stroop task (Mitterschiffthaler et al., 2008). Depressed patients also show less right DLPFC recruitment when required to ignore negative stimuli in an attentional interference task with emotional material (Fales et al., 2008). Moreover, increasing brain activity by multiple sessions of repetitive Transcranial Magnetic Stimulation (rTMS) over the left DLPFC normalized the inhibition of negative emotional stimuli in treatment resistant depressed patients, which was correlated with a decrease in depressive symptoms (Leyman et al., 2011). These results are indicative of difficulties that depressed patients have in activating TP components so as to appropriately execute cognitive control during affective tasks.

A recent meta-analysis reported the effects of pharmacotherapy (e.g. mainly SSRIs) on emotion processing in major depression, supporting abnormal rest-to-affective task transition as specific feature of depression and, in turn, a target for therapeutic interventions (Delaveau et al., 2011). Several findings are in line with the hypothesis that pharmacological treatments effectively targeted both TN-persistence and TP-deficiency: after several weeks of treatment depressed participants displayed reduced activation in SubG, dorsal PCC, and precuneus and increased activation in DLPFC and VLPFC during emotional tasks. An interesting hypothesis to pursue is that antidepressant medication may work by rebalancing TN and TP during rest-to-task transitions.

3.3 *Altered TN-TP anti-correlation in depression*

Zhou et al. (2010) detected an increased degree of anti-correlation between TN and TP in depression using both the PCC/precuneus (TN) and the right DLPFC (TP) as seed regions. This was interpreted as an exaggerated antagonism between these two components, which, the authors argued, may be involved in biased processing of information in depression. For instance, during spontaneous low frequency oscillations, the TP, comprising areas which are known to subserve attention and emotion regulation (e.g. bilateral DLPFC and IPL), might represent active attempts to regulate emotions and deploy attention even without current external stimulation. On the other hand, the fluctuations of the TN (e.g. MPFC, SubG, and PCC/precuneus) may be the neurobiological underpinning of enhanced memory for negative emotional experiences and increased maladaptive self-focus. While the optimal attunement between TN and TP is thought to reflect efficient intrinsic brain organization (Fox et al., 2005), such an exaggerated TN-TP antagonism might reduce the integration between different strands of information (e.g. "internal" vs. "external"), potentially resulting in attention and memory biases. Recently, a study demonstrated a differential role of the rFIC in switching activation between the TN and TP connectivity in depression (Hamilton et al., 2011). That is, during the ongoing anti-correlated TN-TP fluctuations in rest, an increased activity of the rFIC was detected when TN showed a peak in activation while the opposite pattern was found in healthy participants, who showed increased activity of the rFIC when TP activity peaked. The authors suggested that the rFIC plays an affective regulatory function, so that when the negative state subserved by the TN in depression reaches its peak, the rFIC induces an increased activation in the TP to counterbalance this undesired state.

3.4 *Blurred boundaries among neural networks during rest: the "Dorsal Nexus"*

So far, we have delineated specific DMN dysfunctions which occur during rest or in transition to task. Nevertheless, a broader perspective could be fruitful in shedding light on how the TN and TP activity are related to each other and to other neural networks. Recently, Epstein et al. (2011)

demonstrated that when exposed to emotional material healthy people show a clear segregation between the TN (e.g. PCC/Precuneus and MPFC) and emotional processing networks (e.g. insula, amygdala, and ventral striatum). In contrast, in depressed patients these networks are not clearly disentangled but partially overlapping. These results are in line with another study showing that in depression the TN leads the organization of the whole brain during rest, resulting in a perturbation of other neural networks (Zhang et al., 2011). Such problematic failures to clearly segregate networks in depression appear to occur not only interneurally, but also intraneurally within the DMN components. In fact, the TN-TP imbalance in depression may also take the form of an abnormal overlap between TN and TP as this could undermine the attunement between the two resting networks. Sheline et al. (2010) compared connectivity maps of three different resting state networks in depressed and healthy participants. The three networks were the TN (precuneus seed), the TP (DLPFC seed), and the affective network (SubG seed). DMPFC, defined by the authors as the "*dorsal nexus*" to stress the hub role played by this region, was the sole region which distinguished depressed from never depressed participants and was found to be part of all three networks. Moreover, this area was functionally connected with brain regions shown to be crucial in depressive pathophysiology (e.g., DLPFC, VMPFC, superior DMPFC, rACC, PCC, and precuneus). DMPFC activation was also highly correlated with depressive symptoms. DMPFC dysregulation was hypothesized to be the key driver of depression-related impairments, such as attentional problems, increased autonomic responding, and enhanced negative self-focus. The crucial role of this hub area is confirmed by a recent study which shows that SSRIs target the DMPFC by reducing its connectivity to the hippocampus during rest (McCabe et al., 2011).

3.5 ***The DMN as a depression vulnerability marker in at-risk subjects***

Even though research has mainly investigated the role of the DMN in currently depressed patients, some preliminary pieces of evidence suggest that dysfunctions at level of default brain could precede the clinical episode. One approach is to examine close biological relatives, such as

non-affected offspring of depressed parents, as depression in parents is associated with a higher risk of major depression in the offspring (Hoffmann, Baldwin, and Cerbone, 2003). Norbury, Mannie, and Cowen (2011) report that people who have never personally suffered from major depression but have a biological parent with a history of depression show increased TN functional connectivity during rest (e.g. DMPFC and middle temporal gyrus) compared with offspring of non-depressed parents. Beyond the TN hyperconnectivity, other evidence supports the presence of DMN dysfunctions among vulnerable individuals. Confirming the heuristic utility of what we termed as rest-to-affective task transition, Di Simplicio, Norbury, and Harmer (2011) reported the efficacy of SSRIs in normalizing such transition in at-risk subjects. The researchers administered either placebo or citalopram (i.e. SSRI) for 7 days to people with high levels of neuroticism, a personality trait reported to strongly predict the onset of major depression (Kendler, Gatz, Gardner, and Pedersen, 2006). Afterwards, both groups underwent an experiment requiring subjects to classify negative and positive self-descriptors. The analyses revealed that, compared with placebo, citalopram administration significantly decreased activation of the VMPFC and rACC in response to negative self-referred stimuli. This confirms the presence in at-risk subjects of TN-persistence which can be ameliorated by SSRI medication, as reported in currently depressed individuals (Delaveau et al., 2011).

Although more research is recommended, some speculation on DMN in relation to the course of depression is warranted. First, it seems that at-risk individuals could show similar DMN aberrations but to a milder degree, both in rest period and in rest-to-task transition phase. Such a notion has been supported in the context of schizophrenia, another clinical syndrome which demonstrates notable genetic influence and inheritability (for a review, Whitfield-Gabrieli and Ford, 2012). For instance, unaffected siblings of schizophrenic patients show TN hyperconnectivity during rest to a lesser extent than a clinical group, but still greater than healthy controls. Moreover, TP connectivity clearly differentiates clinically affected from unaffected siblings (Liu et al., 2012). These results suggest that it is also possible in depression that at-risk individuals may be characterized by a

neurobiological profile that partially mirrors aberrations observed in clinical depression. Second, such research in at-risk populations suggests that DMN dysfunctions might predict future clinical episodes. In other words, the aberrations within the DMN might precede the onset of major depression. However, it is still a matter of debate by what mechanism the transition from non-symptomatic phases to the first depressive episode occurs. In this context, both theoretical models and empirical research (i.e. longitudinal studies) are needed (Whitfield-Gabrieli and Ford, 2012). Third, given the specific cognitive signature of recurrent depression (marked attentional problems, high levels of rumination, and cognitive reactivity), we argue that DMN aberrations, likely present to a milder extent even before the first clinical episode, become more pronounced with increasing episodes and are associated with recurrence in remitted depressed samples. This proposal is described in detail in the next sections.

3.6 ***The DMN in depression: Theoretical advances***

Several recent attempts have been made to relate different facets of depressive phenomenology to DMN (Hasler and Northoff, 2011; Pizzagalli, 2011). Among others, Northoff et al. (2011) proposed a DMN system theory of depression, focusing on underlying mechanisms of symptoms. They proposed neural hyperactivity during rest as one of the endophenotypes for unipolar mood disorder. In this model aberrant resting brain performance is thus seen as a 'neural predisposition' or susceptibility marker with abnormal rest-stimulus transitions as the final cause of depression. They propose that specific subcortico-cortical systems play distinct roles in the depressive phenomenology. For instance, the rest-related hyperactivity of the rACC, VMPFC, DMPFC, amygdala, and hippocampus is hypothesized to be responsible for sustained negative mood, while decreased TN performance during rest-to-task transition could account for the abnormally high levels of sadness (e.g. Sheline et al., 2009). The deviant perception of subjective time in depressed individuals would be due to an increased rest-related activity of VMPFC, DMPFC, and rACC, whereas hopelessness, which appears closely related to prospection abilities, is linked to reduced

rest-stimulus interaction (e.g. Grimm et al., 2009). Finally, the rest-related hyperactivity of rACC, VMPFC, DMPFC, peri-aqueductal gray, and the dorsomedial thalamus could be responsible for depressive self-focus and rumination (e.g. Berman et al., 2011; Greicius et al., 2007).

It is noteworthy that, despite the increasing efforts to highlight the role of the DMN in depression, the issue of remitted depression is virtually uncovered in literature. Unfortunately, the absence of a theoretical roadmap has so far impeded a systematic and fruitful investigation of the links between DMN and recurrent depression.

3.7 ***The DMN in depression: Summary***

A number of depression-related DMN abnormalities have been reported both during rest and rest-to-task transition. These include (i) increased TN functional connectivity during rest between the MPFC, the PCC, and the SubG (Berman et al., 2011; Greicius et al., 2007, Zhang et al., 2011) with a promising role for areas not universally reported to be part of the TN, such as the hippocampus (Goveas et al., 2011, Zhang et al., 2011) and the thalamus (Lui et al., 2011); (ii) evidence of both TN-persistence (Grimm et al., 2009; Sheline et al., 2009) and TP-deficiency (Mitterschiffthaler et al., 2008; Leyman et al., 2011) following rest-to-affective task transitions with these effects leading to poor attentional control during task involving emotional material. Importantly, these problems with transition from rest seemed to be ameliorated by pharmacotherapy (Delaveau et al., 2011); (iii) an increased level of TN-TP anti-correlation during rest (Zhou et al., 2010); (iv) an altered pattern of TN-to-TP switching with the brain regions thought to drive switching (e.g. rFIC) functioning differently in depressed compared with healthy subjects (Hamilton et al., 2010); (v) less segregation between TP, TN and other resting state networks (Epstein et al., 2011; Zhang et al., 2011) and a strong role for the DMPFC across these networks in depression (Sheline et al., 2010); (vi) at-risk individuals seem to show a depression-like DMN pattern (Di Simplicio et al., 2011; Norbury et al., 2011). Recently, several theoretical

models try to account for different aspects of current depression in relation to DMN (Hasler and Northoff, 2011; Northoff et al., 2011; Pizzagalli, 2011).

4. Cognitive Risk for Recurrent Depression and the DMN

In this section we focus specifically on recurrence of depression in remitted patients, reviewing the literature on cognitive vulnerability factors and describing how default mode dysregulation can provide a unifying explanation of these deficits (Figure.1). As we have described, major depression is characterized by DMN abnormalities. Our model of recurrence is built on the idea that remitted depressed individuals, especially after a history with several depressive episodes, still show most of the DMN aberrations, albeit probably to a lesser extent than in the acute symptom phase. In this sense, the DMN disruptions can be defined as a "depressive scar" (Lewinsohn et al., 1981) and as such are predicted to be influenced by the number and duration of previous depressive episodes (Wichers et al., 2010). Crucially, we suggest that this neurobiological scar is manifest primarily in terms of dysregulation in the pattern of synchronized switching between internally- and externally-oriented attention which marks the normal interplay between TN and TP components of the DMN system. In turn this dysregulation leads to specific and well established cognitive deficits considered as risk factors for recurrent depression; (i) rumination, (ii) impaired attention control, and (iii) cognitive reactivity.

4.1 Rumination and TN-dominance over TP

Rumination has been defined as "behaviors and thoughts that focus one's attention on one's depressive symptoms and on the implications of those symptoms" (Nolen-Hoeksema, 1991, p. 569). The response style theory of depression (Nolen-Hoeksema, 1991) proposes that individuals differ in their reaction to negative mood states and that rumination is a trait-like response style to distress. Individuals engage in depressive rumination because they believe that ruminating about

their mood and symptoms will lead to greater self-understanding. However, rather than leading to increased self-understanding, depressive rumination augments sad mood and negative thinking by focusing attention on current mood (Lyubomirsky and Nolen-Hoeksema, 1995). The harmful effects of rumination may not stem from attention to distress per se, but from internally-oriented attention that is negative, evaluative, and judgmental (Rude et al., 2007).

To assess individual differences in the tendency to ruminate, Nolen-Hoeksema and Morrow (1991) developed the Ruminative Response Scale (RRS). This scale has high internal consistency and acceptable convergent validity (Butler and Nolen-Hoeksema, 1994; Nolen-Hoeksema and Morrow, 1991). Factor analysis of the RRS has identified two distinct subtypes of rumination (Treynor et al., 2003). The first, *reflective pondering*, is a more adaptive form of rumination and reflects the degree to which individuals engage in cognitive problem solving to try to improve their mood. The second, *depressive brooding*, - the degree to which individuals passively focus on symptoms of distress and the meaning of those symptoms - is a more maladaptive form of rumination. Rumination in response to negative mood increases vulnerability to depression. Numerous studies have demonstrated that rumination is associated with depressive symptoms (Treynor et al., 2003) and prospectively with the onset (Nolen-Hoeksema, 2000), severity (Just and Alloy, 1997; Nolen-Hoeksema and Morrow, 1991) and duration (Nolen-Hoeksema, 2000) of depression. The ability to control ruminative thought is associated with recovery from depression (Kuehner and Weber, 1999; Schmaling et al., 2002). Rumination is also associated with cognitive reactivity, one of the crucial predictors of recurrent depression, even when depression levels were statistically controlled (Moulds et al., 2008).

Here we argue that rumination is related to a tendency toward enhanced TN connectivity and TN-dominance over the TP component of the DMN system. In fact, Zhu et al. (2011) reported that in unmedicated individuals with major depression, increased MPFC and SubG connectivity correlated with rumination, measured with the Cognition Emotion Regulation Questionnaire

(CERQ, Garnefski, Kraaij, and Spinhoven, 2001). In line with this, Berman et al. (2011) found increased TN-SubG connectivity in depressed patients during rest periods of a cognitively demanding task. Levels of connectivity between the SubG and the PCC were highly correlated with rumination scores in both clinical and non-clinical sub-samples. The maladaptive ruminative response (i.e. brooding) was correlated with SubG-PCC connectivity across all sub-samples. While healthy participants did not differ in the SubG-PCC connectivity between rest and task-related blocks, depressed patients showed hyperactive connectivity during rest phases and hypoactive connectivity during active blocks. On one hand, these results suggest that when depressed people are left to themselves they are more prone to experience maladaptive internally-oriented rumination. On the other hand, it is possible that during active task periods the enhanced activation of the TP counteracts the TN, which may provide temporary relief from rumination. Moreover, this can result in an abnormal activation of the SubG, implicated, for instance, in reduced likelihood of recovery from depression (Siegle et al., 2006) and an increase in the risk of depression as a consequence of adolescent peer rejection (Masten et al., 2011).

Hamilton et al. (2011) examined the association between TN-TP interplay and rumination using a new approach to data analysis to measure the dominance of one network over the other one. This new index quantifies the number of time periods when the TN BOLD signal is greater than the TP BOLD signal. This allows an estimate of the increased duration of TN-dominance over the TP and an assessment of whether this is reflected by elevated levels of TN functions. Comparing the TN-dominance level in depressed patients and controls, the study reported that this positively correlated with the *depression subscale* – another RRS subscale which along with the brooding subscale measures cognitions characterized by "a passive comparison of one's current situation with some unachieved standard" (Treynor et al., 2003, p.256) – and negatively correlated with the *adaptive reflective pondering* subscale of the RRS in the depressed group. This pattern held also after controlling for brooding and depressive symptoms measured with the Beck Depression Inventory-II (BDI-II, Beck et al., 1996). Interestingly, current findings support this

association between rumination and TN connectivity or dominance only during rest, exactly when task specific regions are intrinsically less activated (Berman and Jonides, 2011). Here we argue that the neurobiological dynamics of rumination (see also Pizzagalli, 2011) are represented by a specific psychological mechanism, namely an aberrant attentional switching in depressed patients which leads to excessive internally-oriented attention (i.e. maladaptive self-focus), a phenomenon subserved by TN hyperactivity. This in turn leads to a failure to use external stimuli to distract from rumination (Disner et al., 2011; De Raedt and Koster, 2010). Increased TP activity to compensate this TN activity could indeed provide environmental stimulation necessary for distraction, efficacious to counterbalance rumination (Huffziger and Kuehner, 2009; Morrow and Nolen-Hoeksema, 1990). Here we propose that this tendency towards TN dominance over TP persists in individuals with a history of depression after recovery from the acute symptoms phase, leaving them vulnerable to rumination during future difficult or stressful times. We predict that remitted depressed individuals, compared with healthy participants, will display an; (i) increased TN functional connectivity during rest, with the SubG being expected to play a major role; (ii) increased TN-dominance over TP during rest; (iii) increased internally-oriented attention during rest. Moreover we propose that (iv) these DMN connectivity indexes and internal attention preference during rest are both correlated with rumination and that (v) connectivity indexes predict, partially mediated by rumination, future depressive relapse in remitted depressed individuals.

4.2 Impaired attentional control, TN persistence, and TP-deficiency in rest-to-task transitions

Attention deficits and impairments in concentration are important diagnostic criteria for depressive episodes (APA, 2000). It has been proposed that impairments in general attentional control functions involved in working memory might drive both these deficits (e.g., concentration) and more specific emotion-related cognitive biases, such as mood-congruent interpretation biases, memory biases, and attentional biases (Joormann, 2005). There is some neuropsychological

evidence suggesting that depression is associated with *general impairments* (valence unspecific) in cognitive control but typically the findings are mixed (for a review, see Joormann et al., 2007), with marked general impairments most often being present in severe depression (Kaiser et al., 2003). Given these inconsistent findings it has been argued that attentional control is particularly hampered in relation to the processing of negative, mood-congruent information (Joormann et al., 2007). Indeed, depression is associated with difficulties in inhibitory processing of task-irrelevant negative material (Goeleven et al., 2006; Joormann, 2004), as well as problematic trial-by-trial updating of negative information in working memory (Joormann and Gotlib, 2008; Levens and Gotlib, 2010). Recently, attentional control has been related to specific cognitive vulnerability factors for depression, such as a rumination (for a review, see Koster et al., 2011) and emotion regulation (for a review, see Joormann and D'Avanzato, 2010). Research indicates that rumination is related to impaired attentional control during the processing of both non-emotional (Davis and Nolen-Hoeksema, 2000; De Lissnyder et al., 2010) and emotional information (De Lissnyder et al., 2010; Joormann and Gotlib, 2008; Lau et al., 2007). Depressive brooding in particular seems strongly related to impaired attentional control. Current research suggests that impaired attentional control plays an important role in depression vulnerability rather than just representing a simple correlate of a depressed state. A number of prospective studies suggest that attentional biases are associated with emotional reactivity and precede the development of anxiety and depression (Beevers and Carver, 2003; MacLeod and Hagan, 1992). In the context of depression, Beevers and Carver (2003) demonstrated that such biases interact with intervening life stresses to predict higher scores on depression seven weeks later. Mood-congruent attentional bias has also been demonstrated after negative mood induction in never depressed offspring at risk for the development of depression (Joormann et al., 2007). Importantly for the current argument, attentional control is reduced during recurrent depressive episodes and this persists even during remission. Electrophysiological markers of cognitive control (N450) have been shown to decrease

linearly with more frequent occurrences of depressive episodes in remitted patients (Vanderhasselt and De Raedt, 2009).

DMN system dysregulation is probably implicated in poor attentional control during task performance. In particular it has been argued that attentional lapses occur when TN activity is not sufficiently attenuated during the transition from rest-to-task and so interferes with task-related activations in TP regions (Sonuga-Barke and Castellanos, 2007). This default mode interference is said to occur when TN activiation exceeds a threshold under which attentional failures are not apparent, but above which the interference could effectively impact on the task. Supporting this hypothesis, Prado and Weissman (2011) demonstrated that during a multimodal selective attention task increased current-trial connectivity between the PCC and the left DLPFC was associated with worse performance (e.g. longer RTs). Moreover, extending the default-mode interference hypothesis, the PCC/left DLPFC connectivity could also predict better performance (e.g. faster RTs) in the next trail, suggesting that current task-unrelated preparatory mental activity can enhance performance of an upcoming task at the cost of worse current performance. Consistent with this, in non-clinical participants longer RTs on a selective attention task were associated with both decreased activation of TP structures, such the right DLPFC, and increased activation of PCC, precuneus, and MTLC, key TN brain regions (Weismann et al., 2006). In a similar way, Polli et al. (2005) found that errors during an antisaccade task were characterized by a failure to deactivate PCC, left superior temporal gyrus, rACC, and DMPFC. Li et al (2007) reported that errors in a stop signal task were preceded by an increased activation of, among other regions, the PCC and precuneus. Interestingly, a recent study stressed that the PCC seems to precede TN-related attentional lapses in that reduced TN deactivation during a speeded Eriksen flanker task predicted errors up to 30s before the error actually occurred (Eichele et al., 2008).These pieces of evidence support a crucial role of *TN-persistence* in attentional lapses, mainly driven by PCC. In addition, Castellanos et al. (2005) reported that subjects affected by ADHD compared with controls showed an increased Intra-Individual Variability (IIV), defined as very long and

relatively infrequent RTs, which temporally mirrored the typical DMN low-frequency pattern (~0.01 - 0.08 Hz). In keeping with this, Kelly et al. (2008) reported that in healthy subjects asked to attend an Eriksen flanker task the IIV, here defined as coefficient of variation (CV), was negatively correlated with the magnitude of the anti-correlation of the DMN components, that is the less the TN and TP were tuned and anti-correlated, the less congruent and consistent the performance was (e.g. increased CV). An increased IIV has been also reported to characterize several clinical syndromes, including depression, and this suggests its possible role as pathological marker (Kaiser et al., 2008). In sum, a wealth of research has indicated that the DMN is associated with impaired attentional control. In particular TN-persistence, TP-deficiency, and reduced TN-TP anti-correlation producing spontaneous fluctuations in performance during task have all been found to be remarkably good predictors of attentional lapses.

Building on the default mode interference hypothesis (Sonuga-Barke and Castellanos, 2007) we argue that reduced attentional control in remitted depressed patients is the result of a failure to properly attenuate the TN network during rest-to-task transitions leading to a disruption of task-related activity in TP regions. We see this pattern of TN-persistence as being due to depression-related alterations during rest, especially TN dominance and increased coherence. This pattern of DMN activity makes it more difficult to effectively switch from rest to task, while at the same time making interference by the TN activity into task-related activity more likely. We therefore predict that remitted depressed individuals, compared with healthy controls, will (i) display TN-persistence in rest-to-task transition, mainly led by the PCC; (ii) show TP-deficiency, mainly at the level of the DLPFC, in attention demanding tasks using non-emotional material; (iii) that TN-persistence during tasks will be predicted by TN-dominance and increased TN functional connectivity during rest, linking excessive rumination with poor attentional control; and (iv) that DMN-related attentional impairments in remitted depressed individuals can predict future depressive relapse.

To date no studies have directly investigated the role of the TN over TP persistence in depressed patients performing an attentional task. There is some evidence underpinning the TP component on attention demanding task performance using non-emotional material. Halari et al. (2009) found depression-related decreases in right DLPFC, using selective attention paradigms (Simon task) and attention switching tasks. A single session of rTMS over the left DLPFC in depressed patients improved performance in an attention-demanding task (task switching) although mood remained stable (Vanderhasselt et al., 2009). This preliminary evidence suggests that currently depressed individuals might show TP-deficiency during rest-to-task transition, even when using non-emotional material. Moreover, remitted depressed individuals showed TP-deficiency, namely reduced left DLPFC activation, after remission (Aizenstein et al., 2009). Nevertheless, there is also some preliminary evidence that in depression and recovery individuals show a similar pattern in attention demanding tasks using emotional material. For instance, multiple sessions of rTMS over the left DLPFC in depressed patients resulted in increased inhibition of negative information (Leyman et al., 2009). Finally, a recent prospective study showed that remitted depressed individuals had impaired cognitive control while switching from angry to neutral faces which predicted rumination as well as depressive symptoms a year later (Demeyer et al., 2012). In conclusion, DMN dysfunction during rest-to-affective task transition appears to be worth deeper consideration, given its possible role in efficiently adjusting to tasks and predicting future depressive relapse.

4.3 Cognitive Reactivity, increased TN connectivity and rest-to-affective task transition

Research on information-processing in emotional disorders has been guided predominantly by Beck's cognitive schema theory (Beck, 1967; Clark et al., 1999) and Bower's associative network theory (Bower, 1981). Beck and colleagues argued that information-processing is guided by schemata, defined as memory structures which, built from previous experiences, contain and organize information about the self, the world, and the future. Depression is characterized by negative schemata involving loss and failure which are thought to bias encoding of information.

Specific information processing biases at the level of attention, interpretation, and memory mediate incoming information processing and subjective (emotional) experience. A fundamental aspect of Beck's cognitive model of depression is that cognitive structures or schemata remain latent until activated by relevant stimuli.

Although broad and general, this notion lies at the roots of the concept of cognitive reactivity, which has been central to the understanding of cognitive vulnerability factors for depression. Cognitive reactivity relates to fluctuations in negative self-attitudes in response to daily (stressful) events (Butler et al., 1994). The crucial question is why certain individuals are or become more reactive to stressors than others. Teasdale (1988) proposed the *differential activation hypothesis* (DAH) to account for this observation. This hypothesis assumes that, after each depressive episode, the link between low mood and negative thinking is strengthened. Therefore, a depressive mood, which can be induced by daily stressors or experimental manipulation, re-activates the negative thinking patterns more easily after multiple depressive episodes. Proposing an association-based mechanism, the DAH can explain the often reported phenomenon that after several depressive episodes even minor hassles can evoke strong depressive symptoms, and a downward spiral of negative thoughts.

Support for this theory comes from studies showing that people who have experienced depression in the past, as compared to never depressed individuals, report more dysfunctional attitudes, negative cognitive biases, and decreased positive biases after negative mood induction (for a review, see Scher et al., 2005). Moreover, some longitudinal studies have shown that the interaction between cognitive reactivity and stress is a significant predictor of the onset of depressive episodes (e.g. Hankin et al., 2004; but see Barnett and Gotlib, 1990). An influential study which supports the role of cognitive reactivity in relapse of depression in remitted individuals found that mood-induced cognitive reactivity significantly predicted relapse over a 18-months interval (Segal et al., 2006). This evidence clearly supports the existence of latent

vulnerability factors in at-risk individuals which are not detected during euthymic phases, but easily activated by stressors.

How is the concept of cognitive reactivity linked to DMN activity? Although direct research on DMN activity in relation to cognitive reactivity is lacking, a relation can be inferred from several lines of research. Cognitive reactivity has been mainly conceptualized as an associative processing between the self, negative mood and negative thinking (Bower, 1981; Teasdale, 1988). Interestingly, the TN circuit overlaps with the brain regions activated during associative conditioning (Bar et al., 2007) and the strength of the association elicited by a stimulus has been shown to be related to the TN activation (Bar and Aminoff, 2003; Bar, 2004; Aminoff et al., 2007). In particular, MPFC, PCC and MTLC (e.g. hippocampus and parahippocampus) play a fundamental role in both basic as well as more complex associative processes (Aminoff et al., 2007; Bar, 2004; Eichenbaum, 2000).

Bar (2009b) proposed a link between aberrations in TN-related associative processing and negative mood (as well as depression). This hypothesis encompasses a bidirectional influence between broad associative thinking and mood. Broad associative thinking is linked to positive affect whereas narrow associative processing is related to negative mood. While the former phenomenon seems to be important in relation to protective factors (cf. the "broaden-and-build theory" of resilience; Fredrickson, 2004), the latter has been applied to depression and related risk factors especially rumination. Bar speculates that during rest MPFC hyperactivity (comprising also the SubG, (see Drevets et al., 2002; Greicius et al., 2007) could dramatically limit activation linked to associative processing in the MTLC. The main psychological outcome of this constraint is both a narrowed associative network and rumination, causing negative mood which in turn reduces the likelihood to broaden the associative links afterwards. Preliminary evidence supporting this hypothesis is provided by an fMRI study that showed enhanced connectivity in the MPFC and MTLC in depression (Berman et al., 2011).

Supporting the link between DMN and cognitive reactivity, the MPFC, the PCC, and the MTLC are all areas involved, albeit to different degrees, in memory and self-related processing (Andrews-Hanna et al., 2010; Cavanna, 2007; Gusnard et al., 2001), functions which are both related to the concept of self-schemata (Beck, 1967). In line with literature showing negative self-evaluation after recovery (Dozois and Dobson, 2001; Seeds and Dozois, 2010), we propose that remitted depressed patients still possess latent negative self-schemata (e.g. negative *mindset*), the neural substrate of which is represented by increased levels of TN functional connectivity during rest. Interestingly, our proposition is partially in line with a recent theory, in which the MPFC, ACC, amygdala and other sub-cortical regions are explicitly invoked to support negative self-schemata in current depression (Disner et al., 2011).

There are many similarities between proposed functions of the DMN, association-based mindset (Bar, 2009a), internal mentation (Buckner et al., 2008) and cognitive reactivity. Not only is cognitive reactivity related to negative evaluation of the self but also to problematic beliefs about the future (i.e, hopelessness; Alloy et al., 1997; Antypa et al., 2010; Barnhofer and Chittka, 2010). According to the Internal Mentation Hypothesis, the TN plays a role in several functions in which mental simulation is required (Buckner et al., 2008), such as temporal self-projection. Interestingly, a recent study shows that currently depressed individuals report a specific impairment in generating episodic details concerning future events (King et al., 2011). Likewise, in remitted depressed and never depressed subjects, hopelessness, an important facet of the cognitive reactivity construct (Van der Does, 2002), predicts lower positive future fluency after negative mood induction (Williams et al., 2008). Note that hopelessness is involved in one`s ability to project oneself in the future and this may be associated with TN abnormalities both in depressed (Grimm et al., 2009) and healthy individuals (Wiebking et al., 2011).

Despite important differences between the internal mentation (Buckner et al., 2008) and association-based mindset hypothesis (Bar et al., 2007), we suggest common underlying

mechanisms. Given the need for past information to both create associative links and mentally simulate new scenarios, it can be argued that both theories rely on memory and memory-related brain regions, such as the MTLC and hippocampus (Buckner, 2010; Perry et al., 2011). Therefore, the TN which may also implicate the hippocampus (Buckner et al., 2008), could provide an overarching influence on these associated functions. An increasing amount of data highlights the role of the hippocampus and memory for TN functional connectivity in the context of depression (Goveas et al., 2011, Hamilton et al., 2010), so that the same pattern can be expected even after recovery. Indeed, as remitted depressed patients continue to show impairments in most of the domains supposed to be embedded in this network, it is plausible that abnormal resting state functional connectivity in the TN plays a crucial role in this specific population.

Providing some evidence for our position, a recent study investigated resting state TN functional connectivity in late-life depression before and after 12 weeks of pharmacotherapy (Wu et al., 2011). Contrary to the findings from a study on mid-life depression (Greicius et al., 2007), this research reported decreased SubG-PCC connectivity in currently depressed patients. This inconsistency with previous research could be due to different data collection and data analysis approaches, as well as to cerebrovascular peculiarities of late-life depression (Alexopoulos, 1997). Crucial to our proposal, pharmacological treatment improved SubG-PCC connectivity but fully remitted depressed individuals continued to differ from healthy participants. Despite differences in the direction of connectivity, this clearly supports the notion that even after gaining recovery remitted depressed individuals display abnormal TN functional connectivity during rest.

As mentioned above, remitted depressed patients, characterized by high levels of cognitive reactivity, do not usually show negative thinking unless they encounter stress in everyday life or undergo negative mood induction in the laboratory (Scher et al., 2005). A manipulation involving negative mood (e.g. listening to a sad music) or self-reference (e.g. recalling a sad autobiographical memory) appears to successfully activate latent schemata as evidenced by

depressotypic negative biases (Phillips et al., 2010). Therefore, rest-to-affective task transition is the ideal context to investigate whether individuals, with high levels of cognitive reactivity, are able to (de)activate the DMN. Mirroring the depression-related *TN-persistence* during rest-to-affective task transition (Grimm et al., 2009; Sheline et al., 2010) and the mindset-stimulus interaction specificity (Bar, 2009a), remitted depressed individuals are supposed to show both *TN-persistence* and *TP-deficiency*. In a recent study, remitted depressed individuals (with three or more major depression episodes) and healthy controls underwent a blocked design fMRI study where sad or neutral video clips were shown (Farb et al., 2011). A remitted depressed subgroup, consisting of patients who relapsed within the following 18 months, showed a statistically significant activation of the VMPFC in response to sad stimuli in comparison with controls. Patients who stayed in remission could not be distinguished from controls in terms of activation in TN. Crucial for our proposal, VMPFC-persistence was found to predict relapse. Moreover, Hooley et al. (2005) reported that, compared with healthy individuals, remitted depressed individuals displayed substantially reduced DLPFC activation, when confronted with negative information (maternal critical remarks). This is in line with the idea that, as for currently depressed individuals (Fales et al., 2008, 2009; Holmes and Pizzagalli, 2008; Mitterschiffthaler et al., 2008; Siegle et al., 2007), remitted depressed individuals also still show TP-deficiency when challenged by negative emotions.

Finally, there is emerging evidence showing that specific therapies for recurrent depression, such as Mindfulness-based Cognitive Therapy (MBCT), may elicit therapeutic effects through their influences on the DMN. In this context mindfulness refers to a particular way of focusing on the present moment characterized by full attention to internal and external contexts, non-judgment and openness to current experience, increased acceptance, and lower experiential avoidance. There is evidence for the value of this treatment as a prophylaxis for recurrent depression (Chiesa et al., 2011). Specifically, MBCT is designed to target the strong associative links between the self and negative thoughts and feelings (e.g. cognitive reactivity) in order to prevent relapse (Segal et al.,

2002). Indeed after MBCT, the relapse rate in remitted patients at high risk for recurrence has been shown to decrease dramatically (Ma and Teasdale, 2004). Two recent studies have found that mindfulness disposition is negatively correlated with cognitive reactivity and that MBCT can directly influence this risk factor reducing its level or deactivating its potential toxic effects on mental activity (Kuyken et al., 2010; Raes et al., 2009). A recent fMRI study found that resting state mindfulness disposition was negatively correlated with TN activation in the MPFC, PCC, temporal cortex, as well as subcortical areas, such as amygdala, hippocampus, and thalamus in healthy participants (Way et al., 2010). Interestingly, the authors suggest that lower TN activation in people with higher levels of mindfulness may reflect weakened links between thoughts, feelings, and the self, supposed to be crucial in dormant negative schemata. After mindfulness training, there appears to be a mindfulness-linked improvement in TN-TP balance in response to sadness provocation (Farb et al., 2010). Following mindfulness training vs. no training, participants displayed increased activation in the DLPFC and SubG as well as increased deactivation in the PCC, left PFC and IFG. Thus, not only does mindfulness seem capable of targeting TN components by reducing its rest-related activation but also by ameliorating aberrations during rest-to-affective task transitions.

In sum, there are several findings consistent with our proposal linking cognitive reactivity with the DMN. First, remitted depressed individuals reporting high levels of cognitive reactivity show negative self-views as well as reduced positive future prospection. Both concepts of self-schemata and future self-projection have been attributed to resting state TN activity (Bar, 2009a; Buckner et al., 2008). This leads to the proposal that remitted depressed individuals show increased TN functional connectivity similar to currently depressed patients. On the basis of this notion we propose that remitted depressed individuals will display increased TN connectivity during rest, which supports the idea of latent negative self-schemata, given the role of TN in internally-oriented attention (Fox et al., 2005), self-related processing (Gusnard et al. 2001), and associative processing (Bar et al., 2007). Additionally, decreased TP connectivity during rest and related

reduced externally-oriented attention might fail to provide exogenous information which may disconfirm and update negative self-schemata. Second, mirroring the mindset-stimulus interaction specificity, remitted depressed individuals are predicted to resemble currently depressed individuals in showing aberrant rest-to-affective task transition. Both TN-persistence and TP-deficiency after emotional challenge have been reported in comparison with healthy people, supporting our proposal that depression-like DMN impairments clearly persist even after recovering. Third, mindfulness-based interventions appear capable of both reducing TN regions activity in rest and improve rest-to-affective task imbalance.

In addition to our previous predictions about (i) enhanced TN functional connectivity during rest, (ii) increased TN-dominance over TP during rest, (iii) increased TN-persistence and (iv) TP-deficiency, we predict that (v) these patterns will be positively correlated with cognitive reactivity measures (as well as rumination and attentional impairment) and (vi) that this abnormal DMN activity will predict, partially via increased cognitive reactivity, future depressive relapse.

5 Conclusion and Future research

In this paper, we introduced a framework which integrates cognitive and neurobiological factors involved in recurrent depression. In particular we propose that specific forms of DMN system dysregulation lead to cognitive deficits that make remitted individuals more vulnerable to the onset of future episodes of depression. We argue that three well-established cognitive risk factors – rumination, poor attentional control, and cognitive reactivity, which have been studied in isolation, have their roots in the TN dominance and hyper-connectivity. These TN features are associated with excessive and maladaptive self-focus and subsequent difficulties in both switching to an extrospective perspective during rest and effectively transitioning into tasks, impairing TP functioning. We suggest that remitted depressed individuals still show aberrant DMN, and that DMN dysfunction may represent a residual neural “depressive scar”, which is linearly influenced by the amount and severity of previous depressive episodes (Wichers, et al., 2010). At the same

time the DMN is proposed to be a good predictor of recovery-related cognitive risk factors as well as future depressive recurrence. Although much more research is needed, initial support for our model comes from a number of sources. First, rumination has been connected in healthy and depressed subjects to increased TN connectivity and TN-dominance over the TP during rest (Berman et al., 2011; Hamilton et al., 2011, Zhu et al., 2011). More specifically, midline structures, such as MPFC, SubG and PCC, play a crucial role in problematic self-related processing such as rumination. Second, attentional control failures, considered to be crucial in depression recurrence (De Raedt and Koster, 2010), are linked to inappropriate DMN rest-to-task transitioning (i.e. TN-persistence and TP-deficiency), mainly guided by the PCC (Eichele et al., 2008), which might be related to the internal-external switch of our attention resources. Third, cognitive reactivity, defined as the ease with which negative latent schemata are activated by appropriate triggers, is thought to be neurobiologically subserved by abnormally increased rest-related TN connectivity (particularly between the MPFC, the PCC and the hippocampus/parahippocampus) as well as by an aberrant DMN rest-to-task transition in the emotional context.

As some of the predictions are quite tentative, we now note several general restrictions that apply to our framework. First, it is noteworthy that there still is ongoing debate about different ways to conceptualize and analyze rest-related task-independent activity. A clear taxonomy of different approaches to investigate resting state is still lacking and a clear consensus on the best way to analyze resting state has not been reached. For instance, studies concerning resting brain activation, rest-related functional connectivity, as well as rest-stimulus interaction, sometimes give inconsistent results likely due to methodological differences (Hasler and Northoff, 2011; Whitfield-Gabrieli and Ford, 2012). Second, the TN-TP anti-correlation is still a topic of debate (Cole et al., 2010). For instance, some authors have argued that apparent antagonism between DMN subcomponents is a technical and methodological artifact (Murphy et al., 2009), whereas most of studies support the idea that there actually is antagonism of function between these two

DMN sub-systems (e.g. Chai et al., 2012; Fox et al., 2009; Liang et al., 2012; Kelly et al., 2008; Margulies et al., 2007). However, the situation is fluid and views may change due to emerging knowledge on TN-TP switching. Third, based on new general developments as well as specific research in depression, future understanding of the DMN in recurrent depression can provide more specific links of different cognitive vulnerability factors to some aspects of this network. Finally, it is important to acknowledge that depression is a complex disorder that can be the outcome of a wide variety of biological, psychological, and environmental factors and the same obviously holds for recurrent depression (Monroe and Harkness, 2011). For example, in most patients increased emotional reactivity is observed, leading to the so called depressive interlock loop (Teasdale and Barnard, 1995), characterized by increased coupling between negative thoughts, emotion, bodily sensations and behavior, whereas other patients show blunted affect and decreased reactivity (see DSM-IV-TR, APA, 2000). Therefore, we argue that specific symptom clusters should be taken into account in future research.

In keeping with this, a change from a syndrome-driven towards a process-based perspective in conceptualizing mental disorders may provide substantial progress in the development of our understanding of psychopathology (Borsboom et al., 2011). For instance, despite notable differences, both depression and schizophrenia share similar DMN aberrations, such as TN hyperconnectivity, TN-persistence, and TN-TP abnormal interplay (for a review Whitfiled-Gabrieli and Ford, 2012). This clearly raises the question about how specific these default brain aberrations may be for each single disorder. It may be that at a general level TN and TP subserve respectively internal and external focus, as we propose in our model, so that mentally-affected individuals showing DMN aberrations are actually characterized by sub-optimal capability of switching between different attentional focuses. However, what still remains unclear is the process through which different forms of psychopathology showing partially similar neurobiological patterns are characterized by different symptom profiles related to the same basic processes, such as dominant internally-oriented attention (e.g. self-focus in depression vs. paranoid ideation in

schizophrenia). Arguably, a dimensional approach could overcome such problem in that certain psychological processes could be fruitfully investigated per se, both in clinical and non-clinical samples (Whitfield-Gabrieli and Ford, 2012). Investigating more basic processes one by one, rather than taking into account an entire and complex syndrome, could indeed enhance understanding of the mechanisms that are crucial in pathological phenotypes, such as the interplay with other networks (Hamilton et al., 2012; Menon, 2011).

Although initial evidence for our framework is promising, more systematic research is required. Below we provide an agenda for future research goals derived from the current framework. The very core of our framework is that remitted depressed individuals still show most depression-related DMN aberrations, which can account for residual symptoms during recovery as well as future depressive recurrence. Hence, the ideal context to test our predictions is by comparing DMN system activity in (medication-free) currently depressed, never depressed and remitted depressed individuals (reporting a different amount of past depressive episodes). To do this, both cross-sectional and longitudinal studies are required. Therefore, as a first step, we provide an overview of important theoretical predictions (Table 1). Afterwards, longitudinal studies which, taking into account all three risk factors at the same time, investigate the potential role of the DMN in predicting future depressive recurrence appear to be the most appropriate further step. In such studies remitted depressed and never depressed individuals are suggested to be recruited and assessed at baseline and follow-ups either with self-report questionnaires and clinician-based interviews. DMN aberrations are thus expected to predict future major depression in the clinical group, partially via cognitive risk factors, whereas this pattern is predicted not to emerge in never depressed individuals. Moreover, we speculate that the DMN contribution to explaining future recurrence might be an overarching predictor which significantly reduces the unique predictive power which each risk factor has singularly. Additionally, the proposed links between cognitive risk factors and DMN may be organized in a hierarchical way so that vulnerability factors do not all predict future recurrent depression to the same degree. Rumination could be the main output of

dysfunctional DMN with both cognitive reactivity and impaired attention control as byproducts of such maladaptive self-focus; but attentional process might also be the core vulnerability factor. Consequently, mediation models appear to be the most appropriate way to map the neural pattern (DMN), psychological functioning (internally-oriented attention) and cognitive deficits (risk factors) in a consistent frame capable of explaining recurrence in depression.

In conclusion, the current analysis motivates a focus on interrelated networks and resting state activity instead of BOLD signal in specific brain structures *per se*. This could indeed be a paradigmatic shift that enhances our insight in the relationship between depression vulnerability and psychological processes, because this relationship implies an interplay between many different brain functions. Therefore, an approach taking into account the associative nature of mental processes and brain functioning provides a promising avenue for future research on inter-individual differences in vulnerability and resilience.

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Table

Table 1. Theoretically-derived research goals

	Risk factor	**Predictions**	**Research Paradigm**
Cross-sectional Studies: *CR, ND and RD*	Rumination	TN increased functional connectivity	rs-fMRI
		TN-dominance over TP	rs-fMRI
		Increased internally oriented attention	rs-fMRI with random internal and external attentional probes
	Impaired Attentional Control	Rest-to-Task transition: • TN-persistence • TP-deficiency	Rest period followed by an attention demanding task using non-emotional material
	Cognitive Reactivity	TN increased functional connectivity	rs-fMRI
		TN-dominance over TP	rs-fMRI
		Rest-to-Task transition: • TN-persistence • TP-deficiency	Rest period followed by an attention demanding task using emotional material. Outside the scanner both self-report questionnaires and experimental mood manipulation are suggested to ascertain cognitive reactivity

CR – currently depressed; **ND** – never depressed; **RD** – remitted depressed; **rs-fRMI** - resting state fMRI; **TN** – Task Negative; **TP** – Task Positive

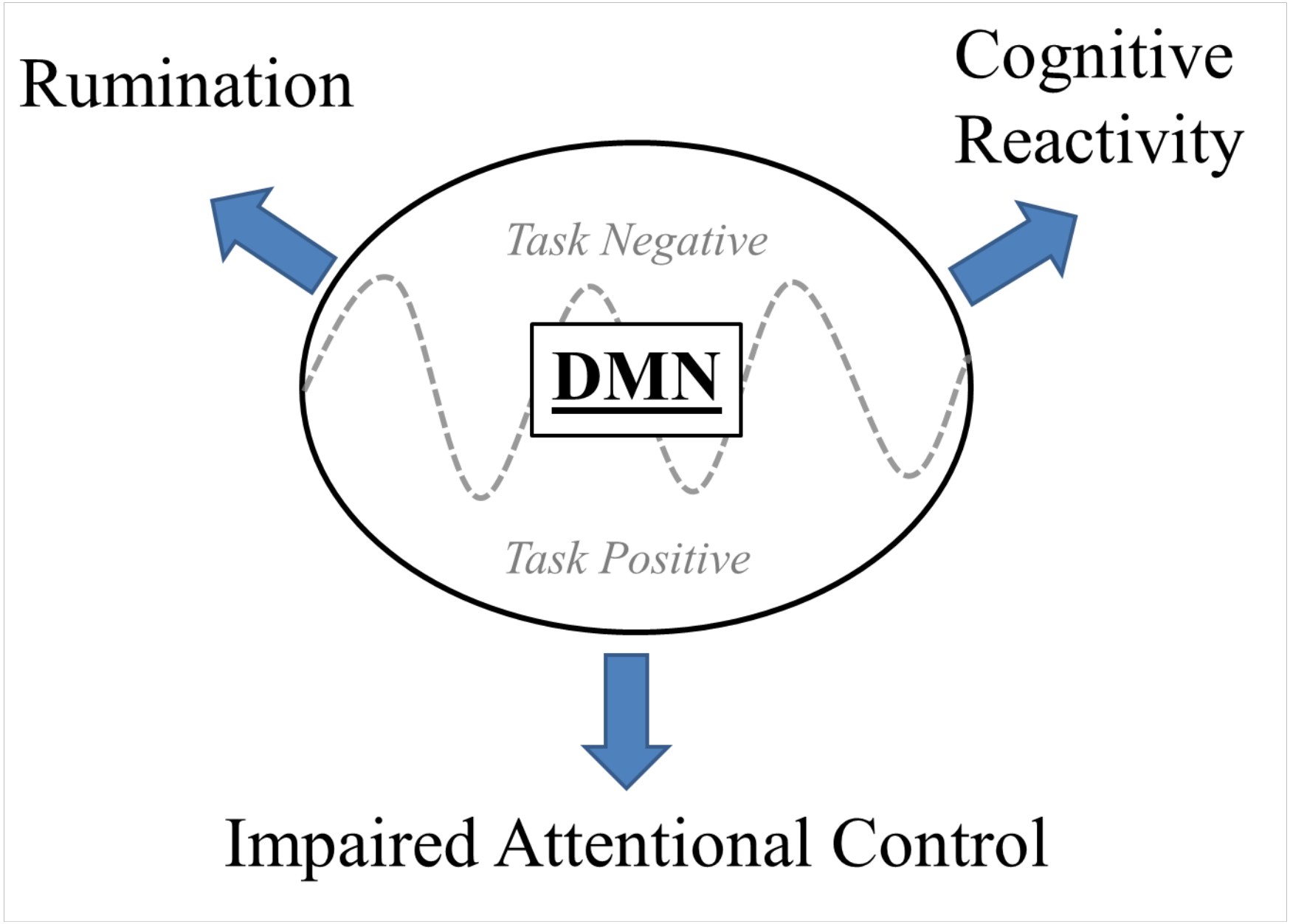
Figure Caption

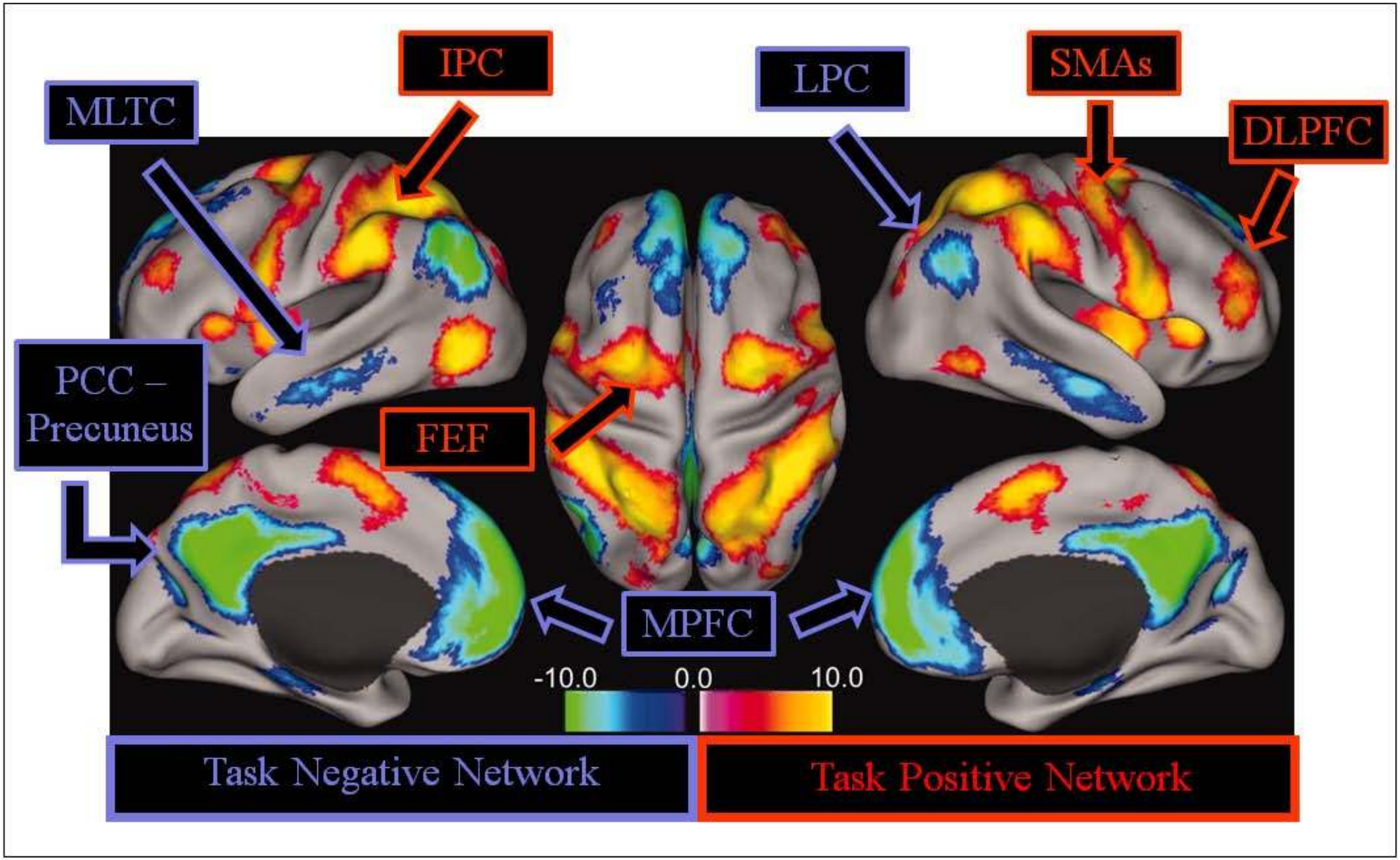
Figure 1: Theoretical framework – Default Mode Network and cognitive risk factors

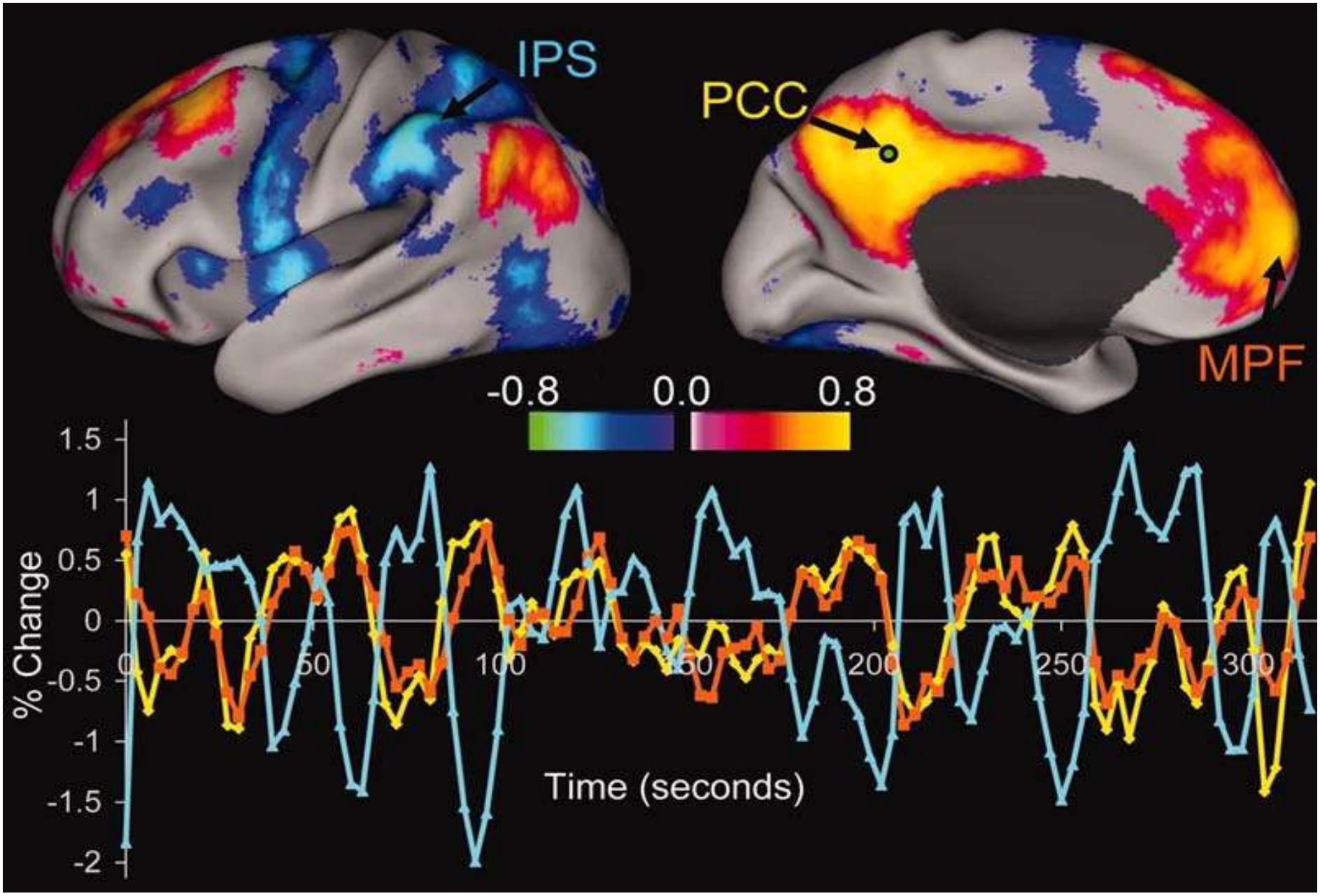
Figure 2: Spatial distribution of BOLD signal fluctuations at rest, representing major areas of the anticorrelated task negative (TN; *green-blue*) and task positive (TP; *yellow-orange*) networks. MPFC: medioprefrontal cortex; PCC: posterior cingulate cortex; MLTC: mediolateral temporal cortex; LPC: lateral parietal cortex; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; IPC: inferior parietal cortex; SMAs: supplementary motor areas. Reproduced and adjusted with permission from Fox et al. (2005) (permissions by Dr. Michael D. Fox and PNAS, copyright 2005, National Academy of Sciences, U.S.A.)

Figure 3: Intrisic anticorrelation between task negative (TN) and task positive (TP) networks in the brain of a single subject during resting state. Posterior cingulate cortex/Precuneus (PCC; *yellow*) and medial prefrontal cortex (MPFC, *orange*) are set as TN seed regions, while intraparietal sulcus (IPS; *blue*) as TP seed region. Both correlations (positive values) and anticorrelations (negative values) are shown for single run and thresholded at r = 0.3. Reproduced with permission from Fox et al. (2005) (permissions by Dr. Michael D. Fox and PNAS, copyright 2005, National Academy of Sciences, U.S.A.)

Figure 4: Rest-to-Task transition in never-depressed and depressed individuals


Rumination
Cognitive Reactivity
Task Negative
DMN
Task Positive
Impaired Attentional Control


IPC
LPC
SMAs
MLTC
DLPFC
PCC –
Precuneus
FEF
MPFC
-10.0
0.0
10.0
Task Negative Network
Task Positive Network


IPS
PCC
MPF
-0.8
0.0
0.8
1.5
1
0.5
0
-0.5
-1
-1.5
-2
% Change
0
50
100
150
200
250
300
Time (seconds)

Depression-unaffected

Rest-to-Task transition

Depression-affected