universität wien

DIPLOMARBEIT

Titel der Diplomarbeit

„Hippocampal Plasticity and Response to Antidepressant Treatment with SSRIs: a longitudinal study “

Verfasser

Julian Provenzano

Angestrebter akademischer Grad

Magister der Naturwissenschaften (Mag. rer. nat.)

Wien, 2015

Studienkennzahl lt. Studienblatt:	A 298
Studienrichtung lt. Studienblatt:	Psychologie
Betreuer :	Univ.-Prof. Mag. Dr. Claus Lamm
Betreuer (extern):	Assoc-Prof. Priv.Doz. Dr. Lukas Pezawas, Dr. Ulrich Rabl

Hippocampal Plasticity in Response to Antidepressant Treatment with SSRIs: a longitudinal study

Julian Provenzano

Abstract

The specific mechanism of antidepressant drugs affecting the monoaminergic system has been an ongoing debate since their discovery in the 1950s. In the last years the proposition that they might alter depressive behavior by influencing neuronal plasticity has gained a lot of empirical support. Especially the hippocampus seems to be one of the key structures involved in this process. However clear evidence from clinical studies is still missing and the effect of hippocampal plasticity on the functional organization of neuronal networks altered in depression is unclear.

In this study structural magnetic resonance imaging as well as automated segmentation of the hippocampus and its subfields was used to show, that responding to treatment with the selective serotonin reuptake inhibitor escitalopram was connected to an increase of the volume of the left hippocampus during the first eight weeks of treatment, that was driven by volumetric changes in the dentate gyrus as well as the CA3 subfield.

Additionally changes of resting state functional connectivity indicated that these structural changes were related to an increase of functional connectivity between the left hippocampus and the anterior cingulate cortex, ventral posterior cingulate cortex as well as left superior frontal gyrus. Besides supporting the neuroplasticity hypotheses, these findings indicate that enhanced neuronal plasticity in the hippocampus is connected to a reintegration of the hippocampus in the default mode network.

Abstract

Seid der ersten Beschreibung einer antidepressiven Wirkung von Medikamenten, die das monoaminerge System beeinflussen, sind die, diesem Effekt zugrunde liegenden, Mechanismen umstritten.
In den letzten Jahren hat die Idee, dass diese Wirkung auf die Beeinflussung von Neuroplastizität zurück gehen könnte starke empirische Unterstützung erhalten. Vor allem neuronale Plastizität im Hippocampus scheint eine zentrale Rolle einzunehmen. Jedoch fehlen eindeutige Belege aus klinische Studien und der Einfluss von hippocampaler Plastizität auf die funktionelle Organisation neuronaler Netzwerke, die während einer Depression verändert sind, ist nicht bekannt.
In dieser Studie wurde strukturelle Magnetresonanztomographie sowie automatische Segmentierung des Hippocampus und seiner Subfelder benutzt um zu zeigen, dass das Ansprechen auf eine antidepressive Therapie mit dem Selektiven Serotonin-Wiederaufnahmehemmer Escitalopram in den ersten acht Wochen mit einer Vergrößerung des Hippocampusvolumens verbunden ist und das diese Veränderung vor allem im CA2/CA3 sowie Gyrus Dentatus stattfindet. Zusätzlich konnte mithilfe funktioneller resting-state Konnektivität gezeigt werden, dass diese strukturellen Veränderung mit einem Anstieg der funktionellen Konnektivität zwischem dem Hippocampus und dem Anterioren Cingulären Cortex sowie dem Posterioren Cingulären Cortex und dem Superiorfrontalen Gyrus verbunden ist.
Neben einer allgemeinen Unterstützung der Neuroplastizitäts Hypothese, deuten die Ergebnisse dieser Studie daraufhin, dass die verstärkte Neurogenese im Hippocampus mit der Reintegration des Hippocampus in das Default Mode Netzwerk verbunden ist.

Contents

1 Theoretical Background **1**

1.1 Neuroplasticity Hypothesis of Antidepressant Action 2

1.1.1 Neurotrophins 2

1.1.2 Neurogenesis 5

1.1.3 The Functional Role of Neurogenesis 7

1.2 A Network Perspective on Depression 10

1.2.1 The Default Mode Network in Depression 11

1.3 Research Question 15

2 Methods **16**

2.1 Participants 16

2.2 Procedure 17

2.3 Imaging Protocol 18

2.4 Data Analysis 18

2.4.1 Preprocessing 18

2.4.2 Sample Characteristics 20

2.4.3 MRI Data 20

3 Results **24**

3.1 Sample Characteristics 24

3.2 Hippocampus Volume 25

3.3 Functional Resting State Connectivity 26

4 Discussion **29**

5 References **34**

1 Theoretical Background

Major Depression Disorder (MDD) (in future referred to as depression) is defined as episodes of persistent negative mood and/or anhedonia connected with additional psychological (suicidal ideation, thoughts of death...) somatic (sleep disturbances, fatigue...) (APA, 1994) and cognitive (preference for negative emotional information...) symptoms (Gotlib & Joormann, 2010).

The World Health Organization (WHO) estimates, that over 350 million people worldwide are affected by depression and that it is one of the "leading causes for disability (...) in terms of total years lost due to disability" (WHO, 2012). In an epidemiological study Chisholm et al. (2013) pointed out that, in order to reduce this number, not only an increased access to treatment but also more efficient treatments of depression are an "evident need"(see also Andrews et al., 2000). So it is not surprising, that since the discovering of the first antidepressants in the 1950s, pharmacological treatment of depression has been a field of extensive research and interest. But, as Baghai et al. (2007) stated, "despite the development of new antidepressants (...) the hope of a better efficacy and clinical effectiveness (...) has not been fulfilled". Antidepressants remain characterized by a rather moderate response rate of about 50% (Trivedi et al., 2006), high relapse rates and a high number of treatment resistance patients (Rush et al., 2006). Katz, Bowden & Frazer (2010) argue that this lack of progress is caused by a limited understanding of "how neural networks relate to individual's behavior, emotions and cognitive functions" in depression and an inadequate concept of antidepressant action.

In the last decades the monoamine hypotheses of depression, proposing that a deficiency of central monoamines is underlying depression, has been a dominant reference point for the development of antidepressive drugs (López-Muñoz & Alamo, 2009). This hypothesis is based on early clinical observations that drugs, inhibiting the neuronal re-uptake or inhibiting the degradation of serotonin and noradrenalin, are reducing depressive symptoms (Schildkraut, 1965; Coppen, 1967). But there have been observations conflicting with the view of a simple relationship between monoamine concentrations and depressive symptoms underlying depression and antidepressive treatment.

Drugs like tianeptine have been shown to have an antidepressant effect without influencing

the serotonergic or noradrenergic system (McEwan, Chattarji & Diamond, 2010) and although decreasing the concentration of serotonin and noradrenalin induces depressive symptoms in remitted patients, it has no pro-depressive effect on healthy subjects (Booij,Van der Does & Riedel, 2003). Also, and maybe more importantly, although effecting the monoamine concentration at receptors almost immediately, several weeks of chronic treatment with antidepressants are needed to alter depressive symptoms (Lavergne & Jay, 2010). So it seems that "rather some gradually developing adaptations to this enhanced neurotransmission (...) mediate drug action" (Nestler, 2002).

Consequently the focus of research trying to explain the mechanism underlying antidepressant action on a cellular level has shifted towards slower, post-synaptic mechanisms (Castrén, 2005). Especially findings connecting antidepressants to the mechanism of neuroplasticity has gained a lot of attention leading to the formulation of the neuroplasticity hypothesis of antidepressant action.

1.1 Neuroplasticity Hypothesis of Antidepressant Action

The neuroplasticity hypothesis of antidepressant action states that antidepressants are working by facilitating neuroplasticity in dysfunctional neuronal networks and thereby enable their reorganization and "repair" (Castrén, 2013). This facilitation is argued to be mediated by the influence of antidepressants on two interconnected mechanism: neurotrophins and neurogenesis.

1.1.1 Neurotrophins

First observations that neurotrophins could play a role in the pathology of depression have been made by Smith & Makino (1995), showing that expression of the brain derived neurotrophic factor (BDNF) was reduced after inducing depressive behavior in rats. This relationship was further highlighted by the observation that injecting BDNF into the hippocampus of a learned helplessness animal model of depression induces an antidepressant-like effect (Shirayama et al., 2002).

Furthermore antidepressant action has been linked to BDNF expression, showing that chronic

treatment with antidepressants leads to an increased expression of the cAMP response element-binding protein (CREB), a transcription factor regulating BDNF expression, in the hippocampus (Nibuya, Nestler & Duman,1996). The link between this transcription factor and depressive behavior was confirmed by the finding, that over-expression of CREB in animal models produced an antidepressant-like effect (Blendy, 2006) and that CREB expression is decreased in the dentate gyrus of animal models of depression (Grønli et al., 2006). Also a causal relationship between antidepressants and BDNF has been supported by the observation, that reduced BDNF-levels as well as reduced tyrosine kinase receptors (trkB; receptor for BDNF) signaling are blocking the effect of antidepressants in animal models (Taliaz et al., 2010, Saarelainen et. al 2003; Monteggia et al., 2004) There has also been some correlative support for this relationship in clinical studies, which suggest that serum levels of BDNF are lower in depressed patients and increased by treatment with antidepressants (Brunnoni et al. 2008; Sen, Duman & Sanacora, 2008). Additionally BDNF as well as CREB levels have been found to be decreased in the hippocampus of suicide victims (see Pittenberg & Dumann, 2008).

However, the cellular effects of BDNF are not a one-way road. There are two variants of BNDF, mature-BDNF (in the future referred to as BDNF) and its precursor pro-BDNF (Autry & Monteggia, 2012). Pro-BDNF has a high affinity to the p75 Receptor, which has been connected to apoptosis (Park & Poo, 2013), while BDNF has the highest affinity to the Tyrosine kinase B receptor (trkB) (Chao, 2003), which is connected to the activation of "pro-survival pathways" (Park & Poo, 2013) and axonal (Reichardt, 2006) as well as dendritic growth (Schinder & Poo, 2000; Horch & Katz, 2002). Interestingly BDNF also shows some affinity to the p75-receptor.

This phenomenon of BDNF, to be able to activate seemingly opposed processes, has been referred to as the "ying-yang hypothesis of neurotrophic function" (Lu, Pang & Wu, 2005). Together with its "stimulus dependent secretion" (Egan et al., 2003), these features make BDNF a prime candidate for mediating experience dependent changes in neuronal systems.

This ability has been nicely demonstrated in an experiment of Maya-Vetencour et al. (2008). Although ocular dominance in rodents is usually only able to change during specific sensitive periods of development, monocular deprivation in adult rodents led to a change of ocular dom-

inance when BDNF was injected in the visual cortex. Without this manipulation no changes occurred. Interestingly the same effects could be reached by orally administering the SSRI fluoxetine (see also Castrén & Rantamäki, 2010).

In order to understand the basic relationship between neurotrophins and depression it is also important to keep in mind, that in animal models depressive behavior is usual induced by exposing animals to stressful situations or directly injecting stress-hormones (for a review see Deusisng, 2006). Consequently stress has been shown to reduce BDNF levels in the hippocampus (Molteni et al., 2009; Neto et al., 2011). But the direction of this relationship seems to be highly specific for different regions and circuits of the brain. (see Pittenberg & Duman, 2008).

In contrast to the hippocampus and prefrontal cortex, stress increases the levels of BDNF in the nucleus accumbens and ventral tegmental area and increasing BDNF levels in this region has been shown to be pro-depressive (Eisch et al., 2003). This rather puzzling result points to a rather complex role of reward circuits in depression and has been proposed by Russo & Nestler (2013) to reflect some form of "strong and inflexible form of learning" (for a review see Russo & Nestler, 2013). In fact BDNF has been shown to be a key factor in long-term potentiation (LTP) and has been connected to several forms of learning, particularly to forms of hippocampus-dependent learning and consolidation (Cunha, Brambilla & Thomas, 2010). Consequently it has been argued that reduced levels of BDNF might be connected to impairments of declarative memory often observed in depression (Cunha, Brambilla & Thomas, 2010),but evidence supporting a relationship between depression and reduced LTP in clinical studies is limited.

One reason for this might me be, that there are no "non-invasive" and ethically acceptable methods available that could be used to manipulate BDNF levels in humans and that it is quite challenging in correlative studies to disentangle the effect of LTP from other variables like motivation as well as other attentional and cognitive deficits. Player et al. (2013) tried to overcome these problems using a paradigm of measuring changing motor evoked potentials (MEP) after a motor learning task. These changes of MEPs are based on a changing excitability of the motor-cortex, which is likely caused by LTP dependent processes that were induced

by the motor task. Depressive patients showed a worse performance on the task as well as smaller increase in the MEPs pointing to a reduced neuroplasticity (Player et al., 2013). But these results have to be considered with some caution. No differences in BDNF serum levels between the healthy and the depressed group have been found and an important confounding factor in this study and especially with regard to the BDNF levels could have been, that the majority of patients in the depressed group were taking antidepressant medication.
Another important role of BDNF in antidepressant treatment, might be its involvement in hippocampal neurogenesis, which is another important source of plasticity in the adult brain (Sairanen et al., 2005).

1.1.2 Neurogenesis

Throughout life new neurons are generated in the dentate gyrus (DG) of the hippocampus (Eriksson et al., 1998, Spalding et al., 2013). The proliferations could be generally seen as following different steps: At first Type I cells (stem cells) divide and generate Type II progenitor cells (intermedior progenitors) as well as Type I cells. The division of these Type II cells leads to Type III progenitor cells (neuroblast). Then the immature neurons are migrating into the granular cell layer, exhibiting enhanced synaptical plasticity for a limited period of time (Ge et al., 2007) and are integrated in the functional circuits of the hippocampus by connecting to the CA3 subfield (Zhao et al., 2006).
Especially findings showing that antidepressant treatment increases neurogenesis in rodents (Malberg et al., 2000) and non-human primates (Perera et al., 2007) have given rise to the hypotheses, that neurogenesis might be involved in the mechanisms underlying response to this treatment. Additionally neurogenesis has been shown to be reduced in post mortem studies of depressive patients (Boldrini et al., 2013) and, as for BDNF, it is well established, that stress reduces the generation of new-born neurons (Mirescu & Gould, 2006). However this relationship might be more complex and dependent on the kind of stress as well as the behavioral response to the stressful situation (see Petrik, Lagace & Eisch, 2012). For example predictable mild chronic stress has been shown to increase neurogenesis (Parihar, Hattiangady & Kuruba, 2011) and the effects of stress in a social defeat paradigm have been shown to be connected to

the coping behavior of the animals (Lagace et al., 2010).

Interestingly also injecting BDNF into the hippocampus of rodents enhances neurogenesis (Scharfman, 2005). This effect of BDNF is relying on the expression of TrkB receptors in progenitor cells and removing those receptors does not only block the effect of BDNF on neurogensis, but also the effect of antidepressants (Bergami et al., 2008; Li et al., 2008). Consequently these findings are raising the question if neurogenesis is causally involved in the antidepressive mechanism or just an epiphenomenon of enhanced BDNF levels.

However a series of studies using cranial radiation to specifically block neurogenesis in the dentate gyrus of rodents are strongly pointing towards a causal involvement by showing that blocking neurogenesis inhibits the effect of antidepressants (Santarelli et al., 2003; Surget et al., 2008; David et al., 2009). In contrast to this finding, studies using pharmacological approaches to prevent neurogenesis yielded conflicting results, but this is likely based on a confounding effect of different time intervals between decreasing neurogenesis and administering antidepressants (see Mateus-Pinheiro et al., 2013).

Antimitotic drugs like methylazoxymethanol (MAM) suppress neurogenesis in a very early stage of proliferation. Studies testing the effect of antidepressants two weeks after injection (for example Bessa et al., 2009), did not find any alteration in the response to antidepressant treatment while the effect of antidepressants was blocked four weeks after administering the drug (Mateus-Pinhero et al., 2013). So it seems that "newborn cells have to reach the age of 4-6 weeks to impact recovery" (Tanti & Belzung, 2013).

Additionally, the role of neurogenesis on depressive symptoms seems to be specific to the remission from depression. Blocking neurogenesis in non-stressed animals does not induce depressive symptoms (Surget et al., 2011) and does not increase the likelihood of developing depressive symptoms when exposed to stress (see Samuels & Hen, 2011; Tanti & Belzung, 2013).

However these findings are still in line with the central hypothesis of a role of neurogenesis in repairing and reorganizing neuronal networks. More problematic seems to be, that while the connection between antidepressants and neurogenesis gains a lot of support in animal studies, only a few researchers explored this relationship in clinical samples and these studies are ad-

ditionally yielding conflicting results.

While some of these studies have observed no relationship between successful response to antidepressants and hippocampal volume (Vythilingam et al., 2004) or have seen such an effect only after a 3-year follow up (Frodl et al., 2008) but not after one year (Frodl et al., 2004) others have found significant changes in the grey matter density of the hippocampus in the first two months of treatment (Arnone et al., 2013) or at least such an effect for the volume of a hippocampal subregion (Schermuly et al., 2011).

Apart from this, there are still many open questions connected to this hypothesis and especially the functional role neurogenesis takes in the remission from depression remains unclear.

1.1.3 The Functional Role of Neurogenesis

Understanding the contribution of neurogenesis to hippocampal functions still offers a great challenge. While there has been progress and manipulating neurogenesis in rodents has been used to connect adult born neurons to learning, memory, cognitive flexibility, exploration behavior and stress regulation, the results are far from conclusive and the basic mechanisms of these effects remain unclear (see Christian, Song & Ming, 2014; Cameron & Glover, 2014). This complexity of results might arise out of the case, that the hippocampus is not a homogeneous structure but consists of several anatomical and functional distinct subfields (see Andersen et al., 2007) and might also be functionally separated along the longitudinal axis, (Fanselow & Dong, 2010) so that the impact of adult-born neurons might be depending on the position along this axis (Wu & Hen, 2014; Kheirbeg, Drew & Burghardt, 2013) as well as differentially impacting different subfields. Additionally, given that neurogenesis is a dynamical process, the specific contribution of adult-born neurons might depend on their age (Nakashiba et al., 2012).

Maybe the best known process in this context is the contribution of neurogenesis to pattern separation, a process allowing the orthogonalized representation of complex overlapping patterns. As proposed in theoretical models (Marr, 1971), this process of pattern separation has been connected to the DG-CA3 circuit (Bakker et al., 2008; Leutgeb et al., 2007). With neurogenesis being limited to the dentate gyrus, it is not surprising that a functional role in pattern

separation has been proposed and in fact, suppression of neurogenesis has been shown to impair the discrimination between stimuli when they were spatially close (Clelland et al., 2009) and enhancing neurogenesis improves the ability to discriminate between similar stimuli (Sahay et al., 2011).

It has been argued that the deficits in pattern separation could underlie overgeneralization, observed in affective disorders, by impairing the ability to distinguish between different contexts of emotional experiences, which could lead to enhanced anxiety and negative mood (Kheirbek et al., 2012). Consistent with this view, suppression of neurogenesis led to an increased overlap of the representation of similar, but not very different, contexts in the CA3 subfield and decreased the behavioral differences between two familiar contexts, when a fear learning task was conducted in only one of these contexts (Niibori et al., 2012), implicating that the learned relationship was generalized to the other context. Also the process of learning to discriminate between two similar contexts in a fear conditioning task has been shown to be impaired after blocking neurogenesis (Kheirbek, Tannenholz & Hen, 2012).

Interestingly, enhancing neurogenesis after context fear-conditioning does induce the clearance of the conditioned relationship (Akers et al., 2014), which is pointing to a role of neurogenesis not only in formation of new memories, but also effecting existing memory traces. Although such a relationship, between adding new neurons to the DG and forgetting, has previously been proposed by computational models (Weisz & Argibay, 2012), predicting a change of weights of the neuronal connection when new neurons are added, the consequences of new neurons impacting existing neuronal networks within the hippocampus are still not clear. Frankland, Köhler & Josselyn (2013) propose that this neurogenesis induced decay of memory traces could be crucial for a balance between memory consolidation, retrieval and forgetting and therefore be important for adaptively and flexible guiding the interaction with the environment.

In fact there have been observations connecting neurogenesis to adapt behavior to changing environmental demands. In an experiment by Burghardt et al. (2012), mice were trained to avoid a stationary shock zone defined by cues in the room. While ablation of neurogenesis had no impact on the initial learning, it impaired the ability to avoid the shock zone after changing

its location. Such a reduced flexibility was also observed in a water maze task (WMT), in which mice had to learn the position of hidden platforms. Mice with reduced neurogenesis needed generally longer to learn positions of the platforms and spend significantly more time in the area of the former learned platforms after changing their location (Garthe, Behr & Kempermann, 2009).

Deficits in cognitive flexibility and episodic memory are common in depression and have been connected to the severity of depressive symptoms (Marazziti et al., 2010; McDermott & Ebmeier , 2009) and especially a tendency towards perseverative behavior was connected to hippocampal volume (Frodl, Schaub & Banac, 2006), what could be seen as a hint that those processes might have a relevance in the pathology of depression. Additionally there have been observations that neurogenesis in rodents could be important for the hippocampus to gain inhibitory influence over the hypothalamic–pituitary–adrenal axis (HPA-axis), which is usually dysregulated in depression. (Snyder et al., 2011; Surget et al., 2011). But the critical question, if and to what extend those observations could be transferred and connected to depression and the action of antidepressants is still unanswered.

As discussed before, blocking neurogenesis is not enough to induce depressive behavior, but most likely critical in recovering from depression. In an analogous manner the reduced hippocampal volumes, commonly observed in patients suffering from depression (Campbell et al., 2004), are most likely not effects of reduced neurogenesis but of the neurotoxic effects of stress (McEwan, 2005) and the role neurogenesis might be important in restoring the hippocampal function and connected neuronal networks. Accordingly increasing neurogensis in depression could go beyond reinstating the “normal” functioning of a “non-stressed” hippocampus, but being part of a reorganization of dysfunctional neuronal networks. But, besides the rather vague proposal, that this process of reorganization could influence networks underlying mood and related cognitive processes (Castrén, 2013), it remains largely unclear in what way the structural and functional organization of neuronal networks is affected and how changes in a limited area could be crucial for recovering from a complex disorder as depression.

1.2 A Network Perspective on Depression

As described before, depression presents itself as a complex and heterogeneous illness. Reflecting this heterogeneity particularly neuroimaging studies, using emotional as well as cognitive tasks, have detected abnormal patterns of neuronal activity in frontal, temporal, parietal as well as subcortical regions (see Willner, 2013; Belzung, Willner & Philippot, 2014) underlying different depressive symptoms as well as structural alterations in regions like the hippocampus (Campbell, 2004) and less frequently the amygdala (Hamilton et al., 2008), prefrontal cortex (Bremner et al., 2002; Botteron et al., 2002) and cingulate cortex (Caetano et al., 2006).

Besides having led to important and influential insights into the pathology of depression, such as the central role of altered cortico-limbic connections (Mayberg, 1997; Siegle et al., 2007) in the pathology of depression or the dopaminergic reward circuits (Russo & Nestler, 2013) in anhedonic behavior, these findings are pointing to an involvement of a rather complex system of alterations in interconnected neural circuits and systems and have made clear, that concepts of depression "based around a single brain region or a single neurotransmitter, are no longer adequate" (Willner et al., 2013). Consequently these observations have given rise to a network-perspective on depression, emphasizing the importance to understand how neural networks are affected by depression on a macro-architecture level.

To study the macro-architectural intrinsic organization of the brain, especially the paradigm of resting-state functional connectivity has gained increasing popularity (Fox & Raichle, 2007). In contrast to task-dependent activity, resting-state studies measure functional connectivity (i.e. interdependent temporal patterns of functional activity) without a specific task (i.e. at rest) over a period of time (Van Den Heuvel & Hulshoff Pol, 2010). In depression, it has also been argued that this paradigm could be additionally valuable, since important dynamics of intercorrelated networks could be missed by measuring short and task-induced, because spontaneous reactions and "neural processes that occur over the course of minutes or hours, as opposed to seconds, are more relevant" (Hamilton, 2013) in a disorder of mood such as depression.

Analysis of functional resting state data has been shown to reliably detect large scale connec-

tivity patterns of correlated and anticorrelated networks, which are most broadly defined as a default mode network (DMN) and task positive network (TPN) (Fox et al., 2005; Golland et al., 2008; Seeley et al., 2007; see also Buckner et al., 2008).

1.2.1 The Default Mode Network in Depression

The core default mode network (DMN) was first described as a network of regions, in which tasks induce deactivation compared to rest (Shuman et al., 1997; Binder & Frost, 1999), including the medial prefrontal cortex (mPFC), ventral posterior cingulate Cortex (vPCC), left and right inferior parietal cortex (IPC) and medial temporal lobe (MTL). This activation at rest and its suppression by goal directed behavior has been shown to be surprisingly stable and robust across a wide range of tasks and modalities (Mazoyer et al. 2001). Additionally greater DMN activation during tasks is connected to worse performance (Eichele et al., 2008) and the DMN has been shown to be increasingly deactivated when tasks get more difficult (Singh & Fawcett, 2008).

However not all tasks reduce activity in the DMN network. Tasks, that are relying on self-generated thoughts rather than external perceptual processes, such as tasks involving autobiographical remembering and episodic memory as well as envisioning the future (Addis et al., 2007) or theory of mind, have been shown to increase activation in default mode regions (Spreng, Mar & Kim, 2009). Consequently the DMN has been argued to be involved in processes with an intrinsic focus of attention and internally-directed or self-generated processes, which are not depending but rather conflicting with the processing of external stimuli (Buckner, 2008; see also Andrews-Hanna, Smallwood & Spreng, 2014)

This dichotomy between internal and external directed processes seems to be also supported by the interaction of the DMN with other large-scale networks, namely the dorsal attention network (DAN) and the frontoparietal control network (FPCN).

The dorsal attention network (DAN), including the frontal eye field, inferior precentral sulcus, superior parietal lobule, superior occipital gyrus and middle temporal motion complex (Fox, 2005; Spreng & Sepulcre, 2013), has been connected to external environment oriented processes (Corbetta & Shulman, 2002). Together with the FPCN, which includes the ante-

rior prefrontal cortex, dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, anterior inferior parietal lobule and anterior insular cortex and is connected to cognitive control and executive function (Vincent et al., 2008), the DAN has been identified as a task positive network (TPN) contrasting activation of the DMN during passive rest, when compared to tasks relying on external perception-dependent processes (Sridharan, Levitin & Menon, 2008; Golland et al., 2008).

Interestingly, while functional activation of the DAN is consistently anticorrelated to activation in the DMN, the correlation and anticorrelation of the FPCN and the DMN or the DAN seems to depend on the kind of task. In tasks known to engage the DMN, the DMN and FPCN are correlated and the DAN and FPCN anticorrelated, while in tasks depending on the DAN, FPCN and DAN are correlated and FPCN and DMN are anticorrelated (Spreng et al., 2013; see also Andrews-Hanna, Smallwood & Spreng, 2014) Consequently, on the one hand, the primary role of the FPCN seems to be generally supporting goal directed processes and has been shown to take a regulating control over the DMN and DAN (Goa & Lin, 2012). On the other hand DMN activation at rest seems to represents at least partly undirected spontaneous self-generated thoughts (Doucet et al., 2011) and mind-wandering (Gruber, 2011; Andrew-Hannah, 2012), which is further supported by the observation that participants, consistently report to experience a variety of mental images, inner speech and autobiographical remembering during phases of DMN activation at rest (Mazoyer et al., 2001).

Interestingly alterations in this dynamic interaction of large-scale networks have been reported in depression. Observations of a dominance of the DMN over the TPN (Hamilton et al., 2011b) at rest and especially that this dominance is connected to depressive rumination (Hamilton et al., 2011b), has led to the idea that an overactive DMN could be underlying this tendency "of thinking perseveratively about one's feelings and problems"(Nolen-Hoeksema, Wisco & Lyubomirsky, 2008). Studies reporting a hyperconnectivity and hyperactivity of DMN regions during rest, particularly the midline structures including the subgenual anterior cingulate cortex (sgACC) and posterior cingulate cortex (PCC) (Greicus et al., 2007; Bermann et al., 2011; Zhou et al., 2010; see also Nejad, Fossati & Lemonge, 2013) are further supporting this proposal, but with other studies are reporting decreased connectivity between different DMN

regions in depression (Anand et al., 2005; Veer et al., 2010) findings are not conclusive.
Besides differences in methodology and confounding effects of medication and other treatment effects, one explanation for the conflicting result could be, that different parts of the DMN could be differently affected in depression. In fact the DMN seems not to be a homogeneous network but consisting of anatomically and functionally distinct subsystems.
Using hierarchical clustering of the functional connectivity between DMN regions during rest, Andrews-Hanna et al. (2010) identified three subsystems of the DMN. A medial temporal subsystem, including the hippocampus, the parahippocampal cortex, the retrosplenial cortex and the posterior inferiorparietal lobe , a dorsal medial subsystem, consisting of the dorsal medial prefrontal cortex, the temporoparietal junction, the lateral temporal cortex, and the temporal pole as well as a midline-core system, including the medial prefrontal cortex and posterior cingulate cortex, that showed strong connections with both subsystems and have been argued to be a functional hub, connecting the other two subsystems. While some differences of the exact regional distribution of the networks exist this basic functional architecture has been generally confirmed by further studies (Doucet et al., 2011; Yeo et al., 2011).
These subsystems also seem to be differentially involved in distinct functional processes. While the medial temporal subsystem has been argued to be especially involved in the retrieval of episodic and contextual memory as well as mental simulation, particularly the simulation of future events, the dorsal medial subsystem seems to be especially important to processes involving social cognition, such as inferring mental states of others and oneself, as well as meta-cognitive processes and the retrieval of semantic and conceptual knowledge (Andrews-Hanna et al., 2010; Andrews-Hanna, Smallwood & Spreng, 2014; Andrews-Hanna, Saxe & Yarkoni, 2014).
Supporting the idea of different alterations of DMN subsystems in depression, Sambarto et al. (2014) observed a hyperactive midline-core DMN, accompanied by a decreased interaction between a ventral (medio-temporal) subsystem and the anterior part of the DMN. Zhang et al. (2011) found an overall increased nodal centrality of DMN regions in depressed patients compared to a healthy control group, that were not correlated with depression severity or illness duration, while a relatively decreased nodal centrality of the left hippocampus was

connected to illness duration and depression severity. Additionally Zhu et al. (2012) reported an increased connectivity of the anterior hub (especially mPFC) and decreased connectivity of the posterior hub (especially PCC/precuneus) and while alterations in the posterior part were more correlated to overgeneralization, alterations in the anterior part were more connected to rumination. Also, using a seed based connectivity analysis, Connoly et al. (2013) found a decreased connectivity between the sgACC and precuneus, that was correlated with depression severity.

While studies investigating resting state functional connectivity in depression offer a great deal of variation of partly conflicting results, there seem to be some repeatedly emerging patterns. First there seems to be a hyperactivity of the DMN which is especially connected to the sgACC, second some studies are pointing to a dissociation of the anterior and posterior hub of the DMN and third, there is evidence for a dissociation of DMN subsystems, which seems to be especially present between the medial temporal subsystem and the anterior hub of the DMN.

Especially the last point is further supported by a reduced integrity of the uncinate fasciculus, a white matter tract connecting the medial temporal lobe and the sgACC, in depression, that is connected to depression severity (De Kwaasteniet et al., 2013). Further highlighting this relationship, Hamilton et al. (2011a) found, using granger causality analysis, that functional alterations of the hippocampus at rest preceded and predicted increased activity in the ventral ACC as well as decreased activity in the dorsolateral PFC, indicating "that the hippocampus has a principal role in affecting depressotypic neural responses" (Hamilton et al., 2011a). Deficits in depression have also been observed in tasks that are known to engage the DMN. Most prominently, in autobiographical memory tasks depression is characterized by a dominance of a semantic over an episodic retrieval of autobiographical events (Williams et al., 2007).

Especially, lesion studies have raised the idea of two, at least partly independent, memory systems underlying those two forms of retrieval (Tulving, 2002) and the hippocampus seems to take a central role in episodic memory. In healthy subjects activity of the hippocampus has been shown to be connected to the vividness and detail of the remembered episode (Addis

& Schacter, 2008; Eldridge et al., 2000) and episodic richness is consistently observed to be reduced in patients with hippocampal damage (St-Laurent et al., 2014; Hassabis et al. , 2007). Similar deficits in depression could also be found in simulating future events (King et al., 2011), an ability that is equally relying on the episodic memory system (Schacter et al., 2012). Consequently, similar functional alterations in depression have been detected in autobiographical memory tasks and tasks involving the simulation of future events (Young et al., 2012; Hach, Tippett & Addis, 2014). These are most prominently involving decreased activation of the hippocampus and parahippocampus as well as medial and lateral prefrontal regions and seem to be more pronounced during future simulation.

In summary, functional alterations of the hippocampus and medial temporal lobe seem to take an important role in deficits of DMN function as well as functional alteration at rest. This is especially interesting because structural changes of the hippocampus are one of the most reliably detected changes in depression (Campbell et al., 2004). But, to my knowledge, there has not been any study exploring the relationship between structural alterations of the hippocampus and the functional changes of the DMN and other large-scale neuronal networks or deficits in autobiographic memory.

However, a relationship between hippocampal volume and specific deficits in episodic memory has been described in early Alzheimer's disease and mild cognitive impairment (Thomann et al., 2012) and other patient groups (Bergouignan, 2011).

1.3 Research Question

As discussed before especially preclinical studies are strongly supporting a role of hippocampal plasticity in the mechanisms of monoaminergic antidepressants and functional alterations of the hippocampus might take an important role in the dysfunction of the DMN in depression. Additionally an increasing number of studies are identifying alterations of the DMN as target of antidepressant treatment (Dichter, Gibbs & Smoski, 2014).

Consequently, the study presented here is following two goals. In the first part of the study the main goal is to replicate the finding of Arnone et al. (2013), that an increase of hippocampal volume is connected to response to antidepressants, by using a volumetric approach (rather

than Voxel Based Morphometry (VBM) as in Arnone et al. (2013)). Besides avoiding critical points in the procedure of VBM, this approach also raises the possibility to differ between effects on different hippocampal subfields. Especially specific changes of subfields CA3 and dentate gyrus, that are, as discussed before, connected to neurogenesis, but not of the CA1, subiculum and presubiculum would further support the notion, that responding to antidepressants is connected to neuronal plasticity that is at least partly caused by hippocampal neurogenesis. In the second part the main goal is to explore the impact of changing hippocampal volume on resting state functional connectivity of the hippocampus.

2 Methods

2.1 Participants

Twenty-seven patients, acutely suffering acutely from major depressive disorder and who had not been currently involved in medical or psychotherapeutic therapy, were recruited at the General Hospital of Vienna (AKH). Further inclusion criteria were (i) willingness and competence to sign the informed consent form voluntarily; (ii) aged 18 to 45 years; (iii) right-handedness; (iv) a DSM-IV diagnosis of a major depressive episode by a structured clinical interview (SCID); (v) a montgomery–asberg depression rating scale (MADRS) score between 20 and 30; (vi) ability to be managed as outpatients; (vii) ability to fulfill the criteria to undergo an MRI scan.

Exclusion criteria were (i) previous or concurrent major medical or neurological illness; (ii) clinically significant abnormal values in routine laboratory screening or general physical examination; (iii) DSM-IV diagnosis of substance dependence within the past year, except for caffeine or nicotine; (iv) DSM-IV diagnosis of schizophrenia, schizo-affective disorder, bipolar disorder, or an anxiety disorder as a primary diagnosis; (v) the use of any psychotropic drug within the last two months; (vi) unresponsiveness of a former major depressive episode to an adequate antidepressant drug dosing of at least 6 weeks duration or any kind of therapy resistance; (vii) a history of severe drug allergy or hypersensitivity or known hypersensitivity to escitalopram; (viii) being acutely suicidal either indicated by a score higher than 6 on item

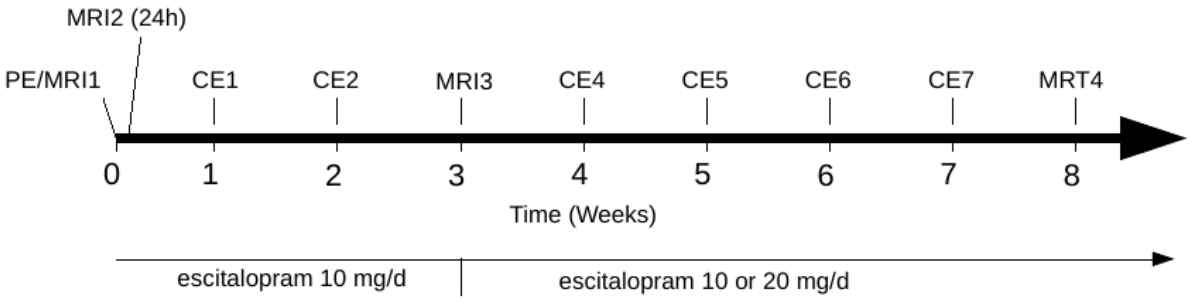

Figure 1: Basic Study Design. PE : Preliminary Eximination, MRI: Examination with MRI Scans taken, CE: Control Examination

10 (suicidal thoughts) on the MADRS or a score equal to or higher than 4 on the hamilton rating scale for depression (HAM-D) 21 (suicidal thoughts) or according to the investigator's opinion (ix) current pregnancy or breast feeding; (x) metallic implants or other contraindications to MRI.

However five participants did terminate their participation in the study after the first MRI scan leading to a final sample size of twenty-two patients. The sample consisted of 11 women and 11 men with a mean age of 31.6 years (SD = 7.6). The mean initial HAM-D score was 19.05 (SD = 4.3). Additionally, one scan of one participant had to be excluded, because of strong movement artifacts and the failing of the segmentation algorithm, and the scans of one participant had to be excluded from the functional analysis because the individual scans of the subject were obtained with different coils.

2.2 Procedure

After a preliminary pychiatric examination and a baseline structural and functional resting-state MRI scan the participants were treated with 10mg escitalopram per day for two months. For ethical reasons and to avoid, that participating in this study lead to a disadvantage for the patients, the responsible psychiatrist was able to increase the doses of escitalopram after three weeks. This was the case for nine subjects. The other MRI scans were conducted 24 hours, 4 weeks and eight weeks after treatment onset. Additionally there have been weekly control examinations (see also Fig.1) and at each examination the symptoms of the patients were rated on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960).

2.3 Imaging Protocol

MRI scans have been acquired on a 3T Siemens TIM Trio scanner with a Siemens 12-channel head coil at the MR-center of excellence, Medical University Vienna. Structural images were obtained by the use of a 3D MPRAGE sequence with TR/TE = 2300/4.21ms, flip angle 9 degrees, inversion time 900ms and a voxel size of 1x1x1.1mm (FoV 240x256x176mm). Functional images were collected in a phase corrected blipped gradient echo (GE), single shot EPI sequence (TR/TE = 42/2000ms, 96 x 96 matrix, 210mm square FOV, 20 axial slices, slice thickness = 4mm, slice gap = 1mm). In order to avoid movement artifacts head movements were restricted using foam pillows.

2.4 Data Analysis

All data analyses were conducted on a Linux system (Red Hat Enterprise Linux 5, x86_64 architecture).

2.4.1 Preprocessing

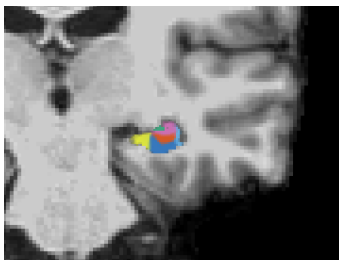

Figure 2: Example for the subsegmentation of the hippocampus

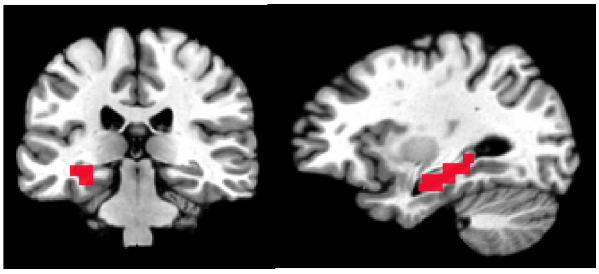

Figure 3: Example for the ROI mask used as seed region in the functional connectivity analysis

Preprocessing of the structural MRI data including registration to Talairach space, intensity normalization, removal of non-brain tissue as well as cortical reconstruction and whole brain volumetric segmentation was performed with Freesurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu), using the Freesurfer longitudinal pipeline (Reuter et al., 2012). The main advantage of this pipeline is the application of subject-specific templates, that are created by co-registering scans from each time-point, what has been shown to create unbiased within-

subject template spaces and images (Reuter & Fischl, 2011).

The whole brain segmentation and labeling of different kind of tissues was performed with a segmentation technique, implemented in Freesurfer and described by Fischl et al. (2002). In order to classify voxels as being part of a specific type of tissue, information of an atlas-based prior probability of a voxel at a certain location in the brain, belonging to a certain kind of tissue, and the probability belonging to a kind of tissue, based on voxel intensity, as well as the intensity of neighbouring voxels are combined. The subsegmentation technique of the hippocampus (see figure 2), developed by Van Leemput et al. (2009) uses a similar logic of combining a probability atlas, of known probabilities in a reference population, and density information in order to define hippocampal subfields using Bayesian inference. Because of the strong priors of the subsegmentation, the relatively small density differences of the hippocampal subfields and the relatively small sizes of these subfields, what makes this technique rather insensitive to change, volumetric changes in this process are defined upon changes of probabilities rather than, as in the whole brain segmentation, number of voxels.

Preprocessing of the functional resting state data including reconstruction, slice-timing correction, rigid-body motion correction, and alignment to the individual anatomical brain using a 12-point affine transformation was performed using AFNI (Analysis of Functional NeuroImages) (http://afni.nimh.nih.gov/afni) (Cox, 2012) within a framework of R software (http://cran-r-project.or/) (Boubela et al., 2012).In order to ensure that magnetization equilibrium was reached, the first five volumes were removed. ANATICOR artefact regression analysis (Jo et al., 2010) with nuisance variables, estimated from white matter (WM) and cerebrospinal fluid (CSF) masks, provided by the FreeSurfer anatomical segmentation, has been applied to the resting state time-series. For temporal filtering a broad frequency band (0.008-0.15 Hz) was used, which has been shown to be highly reliability in resting state fMRI analysis (Braun et al., 2012) and to contain meaningful information, when proper noise regression is used (Boubela et al. 2013). After that, data underwent a spatial Gaussian blur (full width at half maximum (FWHM) = 6mm) followed by warping to Talairach-Tournoux stereotactic space.

Finally functional seed based connectivity z-maps were calculated (see Poldrack, Mumford & Nichols, 2011).

To address possible confounders that may arise out of a fixed seed position and changing underlying brain-structure, individual Freesurfer masks of the left hippocampus of every scan were used to identify the region of interests (ROI) and the seed activation time series was calculated by averaging the signal across all voxels in the masks (see Figure 3). One participant had to be excluded from this step of analysis because the different scans of this subject were obtained with different coils.

2.4.2 Sample Characteristics

To further describe the sample correlations and t-tests were calculated between age, gender and response, defined as the percent change of HAM-D scores over the first eight weeks of treatment.

2.4.3 MRI Data

Generally the data were analyzed within the mixed design model approach (also called multilevel model, hierarchical regression model, random effects model. . .).
To use mixed design models for the longitudinal analysis has some central advantages, such as handling drop out, unequal spacing of measurements and complex structures of the variance-covariance matrices, over the use of repeated-measurement ANOVAs or MANOVAs. (Hox, 2010, Gueorguieva & Krystal, 2004; Hoffmann & Rovine, 2007) Additionally this approach has been proven to have a higher statistical power than more “traditional” accounts like repeated-measurement ANOVAs or MANOVAs in clinical studies (Gueorguieva & Krystal, 2004; Nich et al., 1997) and to be more sensitive and reliable in analyzing structural (Bernal-Rusiel, 2013) as well as functional MRI data (Chen et al., 2013).

Structural MRI The statistical analyses of the MRI data were conducted using R (R development core Team, 2013) with the ”nlme-packge” (Pinerho et al, 2013) for the estimation of the mixed design models.
The aim of the first analysis was to explore the structural change of the right and left hippocampus over different measurements and how this change is related to antidepressant treatment

response. Within the mixed design approach the basic logic of such a situation is modeled by analyzing differences of within-subject "slopes of change over time, using [...] variable[s] predicting differences in the slopes"(Hox, 2010).

Not only, but especially when faced with a rather small number of subjects and few observations for every subject, a common problem of multilevel models is, that the number of parameters easily gets very large, the model very complicated and difficult to estimate, what could also lead to "overfitting". In order to prevent thiese difficulties the models were, as generally proposed, build in a steps-wise process (Snijder & Bosker, 2011; Hox, 2010).

As a first step a basic model of the time trajectory, describing the change of volumes over time had to be carefully fitted. In order to model this change over time and following the basic assumption, that potential differences of volumes between measurements at different time points would reflect an underlying continuous time trajectory, a continuous variable coding for the time points of measurements was included as a predictor in both models (see also Bernal-Russiel, 2013). Using this "linear regression paradigm" allows to estimate the volumetric changes as a linear function of time. Following the nested character of the observations a second level was defined by including a random intercept for the subjects. This basic model could be formally described as:

$$y_{ij} = \beta_0 + \beta_1 T_{ij} + u_{0j}$$

Where T_{ij} represents the time point of a measurement i of a subject j while β_0 represents the overall (mean) intercept and u_{0j} the group (in this case Subject) effect or level two residual. So the intercept is specific to a subject and can be understood as being estimated by an equation at a "second level". In the case described above as:

$$\beta_{0j} = \beta_0 + u_{0j}$$

However in this model the slopes are still fixed, assuming the very unlikely case that the

relationship between time and volume is the same for all subjects. In order to relax this assumption also a random slope for the time variable (with u_{1j} representing the slope residual) was included.

$$y_{ij} = \beta_0 + \beta_1 T_{ij} + u0j + u_{1j} T_{ij}$$

With this extension of the model, the slope of the regression, between time and volume, for one subject is the sum of the mean slope (β_1) and the subject specific slope residual (u_{1j}).
Given the longitudinal design, especially two further considerations in this step had to be taken into account. The first one is the question about the order of the trend. Although assuming a linear relationship between the time variable and outcome (and thereby a linear time trajectory) usually fits a local trend of a limited period of time very well, also quadratic and cubic (and if possible higher) trends should be taken into account (Bernal-Rusiel, 2013). This was done by estimating models, assuming different trends using the poly() command in R, and comparing them with a likelihood-ratio test (Pinhero & Bates, 2010), which showed no significant improvement of the model fit for both models.
The other question, that had to be taken into consideration, was that the assumption of a simple structured variance covariance matrix of the dependent variable could be violated. In a model as fitted here, repeatedly measuring the volumes would suggest, that these observations are correlated what might lead to correlated residuals and an underestimation of standard errors. But graphically exploring the autocorrelation of the model residuals using the Autocorrelation Function (ACF) (Pinhero & Bates, 2000) showed no (positive) autocorrelation and including autoregressive correlation structure to model the dependencies among observations (Pinhero & Bates, 2010) did not improve the general fit of the model. In a next step, the basic model was extended by adding further explanatory variables. The second-level (time invariant) variables treatment response, defined as the percent change of HAM-D scores (Hamilton, 1960) between baseline and after eight weeks of treatment and the mean estimated Intracranial Volume (ICV), to control for the effect of general differences in brain size, as well as the cross-sectional interaction effect of response and time and all other interaction effects were forced

into the model. Significant second level main effects can be understood as explaining differences (variance) in the intercept between subjects while cross-sectional interaction effects represent the change of the slope of one predictor, when the other predictor changes (see Hox, 2010), in this case the change of the slope of the time trajectory when the response variable is changing. Gender and Age were not included in the model for two main reasons. On the one hand especially in regard to the rather small sample size it was important to keep the model (and the number of parameters) as simple as possible, on the other hand, biasing the results was unlikely because the analysis was mainly about the change within subjects. Because the relationship between gender and response was significant on a trend level ($t(16) = -1.82$ $p = 0.09$), additionally a model with group mean centered predictors (see Snijder & Bosker, 2011) for gender was estimated to exclude a possible confounding effect of this relationship.
Then also the issue of possible heteroscedasticity had to be addressed. Assuming that the central hypothesis, that responding to the treatment with antidepressants would result in structural changes of the hippocampus while patients not responding would show no differences is true, it could to be seen as likely that the variances of hippocampal volumes of patients responding to the treatment would be higher than the variances of patients not responding. However exploring the residuals of the model graphically did not point to heteroscedasticity and including a term to model potential heteroscedasticity did not improve the model. Finally all resulting p-values were corrected for multiple comparison using the Bonferroni-Holm method (Holm, 1979).
In order to further explore the significant change of volume of the left hippocampus models for the volumes of the left hippocampal subfields including the dentate gyrus/CA4 , CA2/CA3, CA1, subiculum and presubiculum were estimated. For all these models the model, build for the left hippocampus, was taken as a starting point and then checked for central assumptions including a normal distribution of residuals on every level, uncorrelated residuals and heteroscedasticity, which were generally not violated. However one subject showed unexpectedly high variations in the subiculum volume and was excluded from this analysis.

Functional Resting State Connectivity he aim of the second part of the analyses was to explore the relationship between changes in hippocampal volume and resting state functional connectivity of the hippocampus. Consequently the basic model included the volume of the left hippocampus, which was corrected for ICV, using the residual method (Sanfilipo et al., 2004), a random intercept for every subject and a random slope for the corrected hippocampal volumes. Because the models had to be estimated for every voxel of the z-maps (see 2.4.1) no stepwise model building process was possible and therefore age as well as gender and all possible interaction effects were forced into the analysis as covariates of no interest. The voxel-wise analysis was conducted with AFNI (3dLME) (Chen et al., 2013). One scan had to be excluded, because it presented an unexpected high outlier (but not the other scans of the same participant), which only had an marginal effect on the results.

The results were cluster-wise corrected for multiple comparisons using Monte Carlo simulations (3dClustSim,10,000 iterations, smoothness estimation with 3dFWHMx, dimensions: 74 9 87 9 69 grid, 2.19 9 2.19 9 2.19 mm3,a minimum cluster size of 256 voxels yielded a corrected p value of 0.05) at a voxel-wise threshold of p = 0.01. This threshold was chosen because the primary interest was the interaction with rather large neuronal networks. Corrected clusters with p-values of 0.05 or smaller were considered significant and clusters with a corrected p-value smaller than 0.1 were considered significant on a trend level.

3 Results

3.1 Sample Characteristics

Patients in the sample showed no significant difference in age between male and female participants (t (17) = 1.00, p = 0.33) and there was no significant relationship between age and response to the treatment, defined as the percent change of HAM.D scores of the first eight weeks of treatment, (r = -0.15, t (20) = -0.69, p-value = 0.50). Differences in response of men and women were significant on a trend level (t (16) = -1.82, p = 0.09), with men responding better than women.

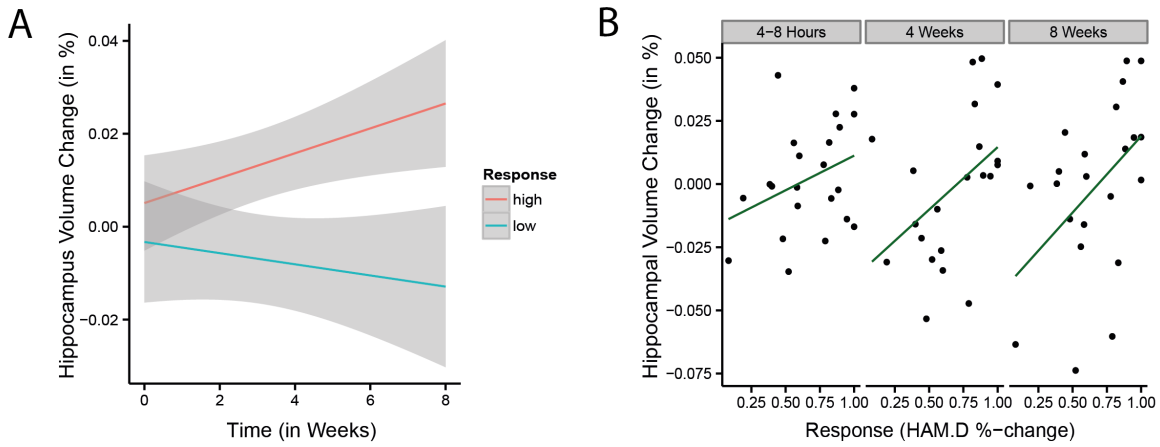

Figure 4: (A) Mean trend of hippocampal volume change of the 25% highest and 25 % lowest responding participants with 95% confidence interval bands and (B) interaction effect of treatment-response and time on hippocampal volume change.

3.2 Hippocampus Volume

The longitudinal analysis of hippocampal volume showed a main effect of intracranial volume (ICV) on the volume of the left (b = 317.86, t(18) = 3.61, p_{corr}= 0.004, SD = 88.09 (95% CI: 132.79; 502.92)) as well on the right hippocampus (b =321.919, SD = 98.85 (95 %CI: 114.24, 529.59), t(18) = 3.26 ,p_{corr} = 0.0044) . The interaction effect of time and response to antidepressant treatment was only significant for the left hippocampus (b = 30.444, SD = 12.30 (95% CI: 5.83; 55.05) , t(61) = 2.47, p_{corr} = 0.032 (p = 0.016)) (see figure 4) but not for the right hippocampus (b = 11.34, SD = 14.07, t(61) = 0.81, p = 0.42). There were no other significant effects ($p > 0.4$, see table 1). In order to test for an confounding influence of gender, the model was re-estimated with variables, that were group mean centered for gender, which did not change the results (left hippocampus: time x $response_{demean}$ (b = 30.04, SD = 11.50 , t(61) = 2.61, p = 0.01)). Consequently only the subfields of the left hippocampus were further investigated. ICV significantly predicted the volume of all subfields (see table 2) but the interaction effect between time and response was specificly significant for the CA2/3 (b = 82.61, SD = 37.91 (95% CI: 6.81; 158.42), t(61) = 2.18, p = 0.033) and DG/C4 (b = 41.549, SD = 19.16 (95% CI: 3.23,79.87), t(61) = 2.17, p = 0.034) (see figure 5). No other effects reached significance (see table 2).

3.3 Functional Resting State Connectivity

In the analysis of the relationship of hippocampal volume change of the left hippocampus on functional resting-state connectivity of the left hippocampus two clusters reached significance (see figure 6). The first included the left superior frontal gyrus (SFG) and left anterior cingulate cortex (492 voxels, $p < 0.01$) with a peak in the left SFG (x = 16, y = -62, z = 12). The second cluster included bilaterally the ventral posterior cingulate cortex (275 voxels , $p < 0.05$) with a peak in the left ventral PCC (x = 8, y = 46, z = 19). A third cluster in the right ACC was significant on a trend level (263 voxels, $p < 0.1$) with a peak in the right ACC (x = -16, y = 42, z = 1) (see figure 6).

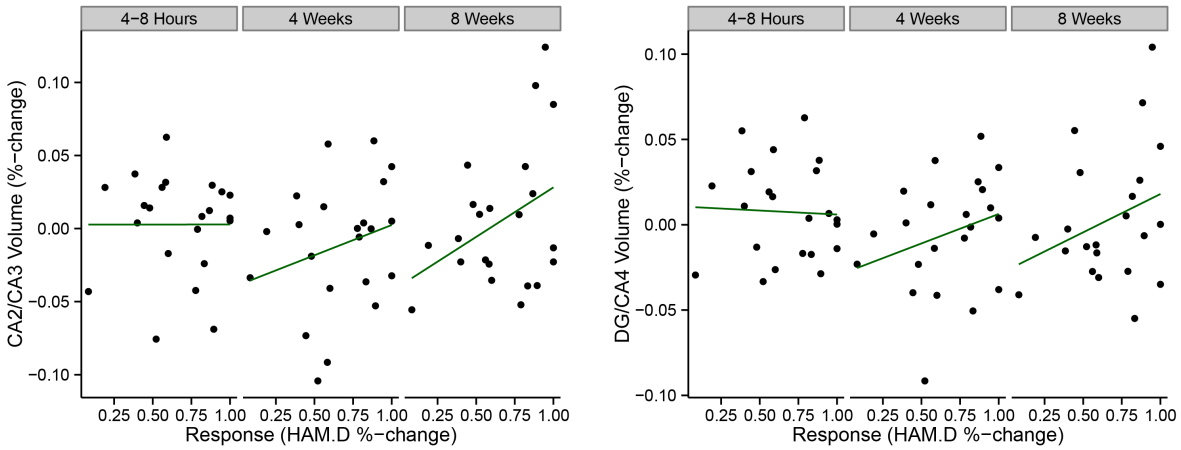

Figure 5: Interaction effect of treatment-response and time on CA2/CA3 and DG volume change

3.3 Functional Resting State Connectivity

In the analysis of the impact of hippocampal volume change of the left hippocampus on the functional resting-state connectivity of the left hippocampus two clusters reached significance (see Figure 6). The first included the left superior frontal gyrus (SFG) and left anterior cingulate cortex (492 voxels, $p < 0.01$) with a peak in the left SFG (x = 16, y = -62, z = 12). The second cluster included bilaterally the ventral posterior cingulate cortex (275 voxels , $p < 0.05$) with a peak in the left ventral PCC (x = 8, y = 46, z = 19). A third cluster in the right ACC was significant on a trend level (263 voxels, $p < 0.1$) with a peak in the right ACC (x = -16, y = 42, z = 1) (see Figure 6).

Table 1: Effects of time, treatment-response and intracranial volume (ICV) and Interaction effects on hippocampal subfields

			left				
	Left Hippocampus	Right Hippocampus	CA4/DG	CA2/3	CA1	Subiculum	Presubiculum
Time	−9.95	−9.18	−20.29	−15.79	−17.05	−43.75	3.81
	(12.25)	(14.09)	(19.07)	(37.73)	(15.38)	(23.68)	(23.91)
Response	−0.74	−23.22	−18.35	−110.09	−116.16	48.30	39.11
	(89.88)	(100.57)	(118.91)	(234.66)	(65.59)	(113.64)	(97.11)
ICV	317.86**	321.92**	339.55**	649.73*	231.83**	433.84**	254.88*
	(88.09)	(98.85)	(116.54)	(234.66)	(64.28)	(111.22)	(95.45)
Time:Response	30.44*	11.34	41.55*	83.61*	8.87	−24.29	7.06
	(12.31)	(14.07)	(19.16)	(37.91)	(15.45)	(23.51)	(23.87)
Time:ICV	−5.13	1.02	−18.01	−14.5	−15.76	−2.95	18.72
	(12.06)	(13.83)	(18.78)	(37.15)	(15.14)	(23.01)	(23.46)
Response:ICV	50.45	49.52	37.12	19.61	−42.98	76.16	−8.78
	(117.77)	(131.36)	(155.80)	(313.74)	(85.94)	(152.74)	(126.85)
Time:ICV:Response	13.59	−11.98	43.15	65.69	8.37	-56.54	4.41
	(16.13)	(18.38)	(25.11)	(49.67)	(20.24)	(31.59)	(31.17)
Constant	4233.43**	4329.35**	4397.39**	7821.07**	2623**	5299.87**	3960.14**
	(89.43)	(100.74)	(118.31)	(238.23)	(65.27)	(114.49)	(97.28)
Observations	87	87	87	87	87	83	87
Subjects	22	22	22	22	22	21	22
Log likelihood	−518.23	−517.53	−538.86	−594.38	−526.79	−539.11	−566.83
Akaike Inf. Crit.	1060.48	1059.06	1101.72	1212.76	1077.55	1102.21	1186.26
Bayesian Inf. Crit.	1088.91	10087.64	1130.16	1241.19	1105.99	1130.18	1157.68

Note: Volumes of Hippocampus and Hippocampal Subfields have different units (see 2.4.1); $^{*}p<0.05$; $^{**}p<0.01$

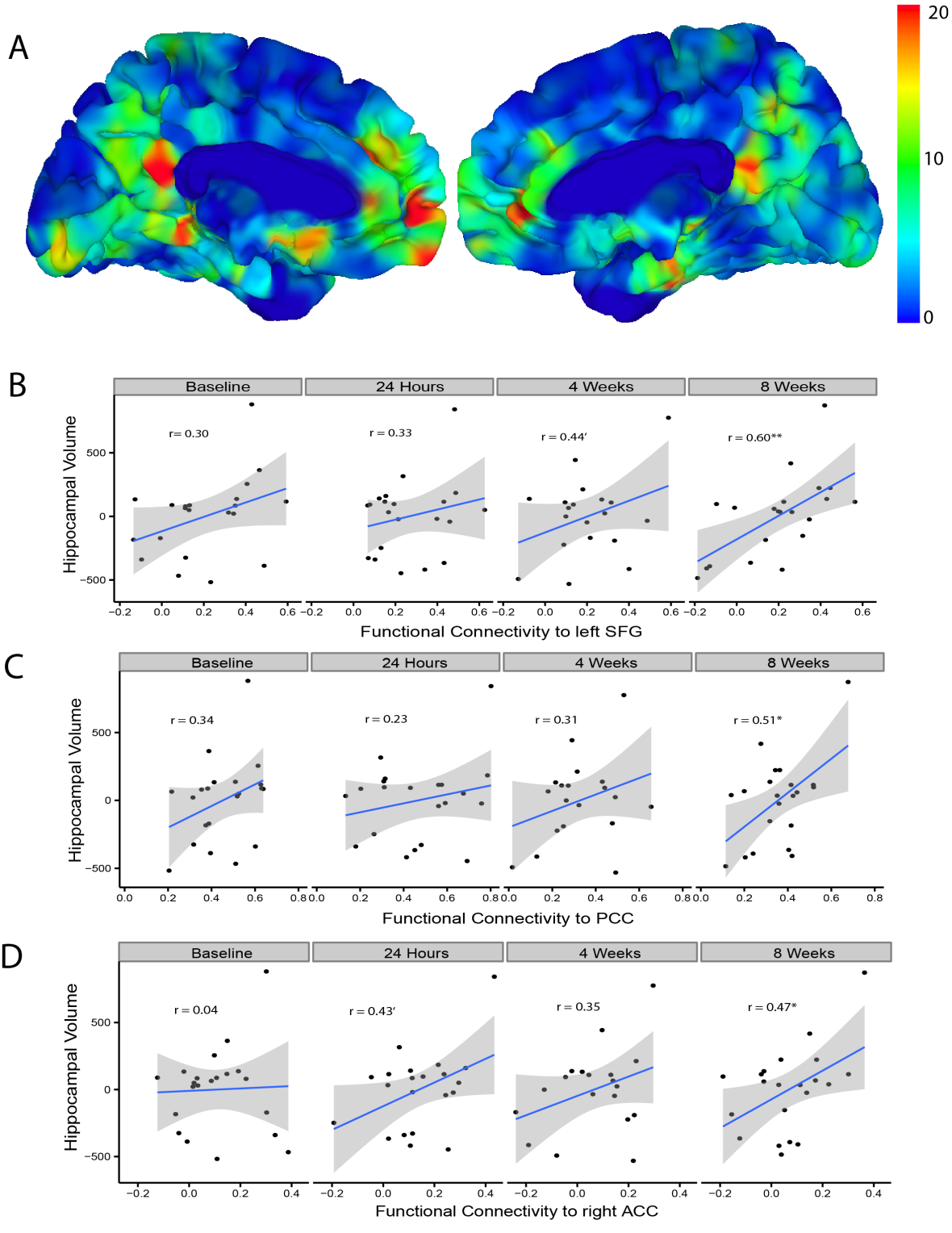

Figure 6: (A) F-value map of the effect of left hippocampal volume on functional connectivity of the left hippocampus and (B-D) plots of this effect in the peaks within significant clusters (B) SFG [16,-62,12] (C) left ventral PCC [8,46,19] (D) and right ACC [-16,42,1]. For better visualization purposes of the within-subject effect the relationship was plotted for every measurement point and correlation coefficients with significance levels ($'$ $p < 0.1$, $*$ $p<0.05$, $**$ $p<0.01$) were calculated

4 Discussion

The present study provides further evidence, that a responding to antidepressant treatment is connected to an increase of hippocampal volume. Especially the finding, that this change was driven by the CA3 and dentate gyrus subfields, is supporting the claim, that this relationship is related to enhanced neurogensis in patients responding to treatment and therefore in line with the plasticity hypothesis of antidepressant action. However, this finding is only correlative and allows no determination of the direction of the influence. Besides arguing that neurogenesis leads to responding to treatment with antidepressants, it would also be possible that remitting from depression could lead to increased neurogenesis. This could especially be the case because environmental enrichment is known to enhance neurogenesis (Kempermann, Kuhn & Gage, 1997) and remitting from depression could be in some way seen as a situation where a deprived environment and is left for a more stimulating one. But there is converging evidence of a causal relationship between enhanced neuroplasticity and neurogenesis in animal models (Tanti & Belzung, 2013) and although animal models of depression might not depict the whole picture of depression, they have been highly validated by drugs affecting the monoaminergic system (Deusisng, 2006) and even if their usability in testing new drugs or making predictions about the aetiology of depression might be questionable, they should be an adequate model for the basic mechanisms of monoaminergic antidepressants.

However, it has been argued that antidepressants enhance neuronal plasticity and facilitate a repair of altered neuronal networks in depression in interaction with experiences (Castrén, 2013) and describing the interaction of this processes with environmental resources will be very important to further understand this process and could especially be important for understanding why some patients are responding or not responding to a placebo treatment.

A very interesting point in this context is set by observations that BDNF might not only mediate the enhancement of neurogenesis by antidepressants (Li et al., 2008) but also the influence of an enriched environment on neurogenesis (Rossi et al., 2006). Accordingly effects of antidepressant therapy and environmental stimulation could share some central features and may have additive effects in combination. It might also explain why response to placebos and antidepressants share some central features, particularly the delayed response, and why the

placebo effect is influenced by the extend of social interaction during treatment (Posternak & Zimmerman, 2007; see also Castrén, 2013).

Conflicting with previous results (Arnone et al. , 2013; Boldrini et al., 2013) there was only an effect present for the left hippocampus. While reduced hippocampal volume in depressed patients is regularly and consistently described, there is some variance in the lateralization of this effect. Some studies observe reduced hippocampal volume only in the left or right hippocampus, while other find a bilateral reduction (see MacQeen & Frodl, 2011). Although there are some experimental results from animal models, that the effect of stress and inducing depression-like symptoms in this animals might be more pronounced in the left hippocampus (Luo et al., 2014), the factors underlying these different findings are unclear.

However, other studies did not find an effect of antidepressant treatment on hippocampal volume at all or only after three years after treatment (Vythilingam et al., 2004; Frodl et al., 2008; Frodl et al., 2004) Besides being effects of different segmentation-protocols or low statistical power, because of small sample sizes, it could also be important, that in a timespan of one or three years, there could be a cumulating influence on hippocampal volume by a variety of factors and also the relationship between scores on a depression scale after one or three years of the beginning of the original treatment might reflect many factors apart from the success of this treatment. Especially when considering that the neuronal plasticity hypothesis would predict changes in the hippocampal volume at the time of response to antidepressant medication, it seems quite possible that the time between the baseline and follow up measurement in the studies by Frodl et al. (2004) and Frodl et al. (2008) has just been too long to observe a coherent effect.

The other central finding of the study presented here is, that increased hippocampal volume is connected to an increased functional resting state connectivity of the left hippocampus with the anterior cingulate cortex (ACC), ventral posterior cingulate cortex (vPCC) and superior frontal gyrus (SFG). These regions are generally known to be activated by a variety of tasks involving autobiographical memory, future thinking and social cognition (Spreng, Mar & Kim, 2009) and the ACC as well as SFG seem to be especially important for self-referential processes (Summerfield, Hassabis & Maguire, 2009). In this context the role of the ACC has been

argued to be especially the assignment and generation of affective meaning and significance (Roy, 2012; D'Argembeau, 2013). However most interestingly the ACC as well as the PCC, are the main hubs of the DMN and have been described as a midline core network connecting the subnetworks of the DMN (Andrews-Hanna et al., 2010; 2014). In some studies the SFG is also described as being part of this midline core system (Yeo et al., 2011; Andrew-Hanna et al., 2014). Consequently an increased connectivity with these regions could be seen as a reintegration of the left hippocampus into the DMN.

This finding is in line with studies showing a dissociation between the medial temporal subsystem of the DMN and the DMN at rest in depression (Sambarto et al., 2014; Zhang et al., 2011) and an reduced engagement of the hippocampus in autobiographical memory tasks connected to depression (Young et al., 2012 ; Hach, Tippett & Addis, 2014). As Hach, Tippet & Addis (2014) argue, the findings are pointing to the possibility that there is not only a dominance of the DMN (Hamilton et al., 2011) and therefore a dominance of internally-oriented processing, but also an alteration of the content of those self-generated thoughts. This is especially interesting because the overactivity of the DMN at rest has been connected to depressive rumination (Hamilton et al., 2011), but only an increased preference to engage in self-generated thought and mind wandering, might not in itself be maladaptive and lead to depressive rumination (Smallwood & Andrews-Hanna, 2013). Moreover it has been shown, that maladaptive rumination, which increases negative mood, is connected to a content of rumination, that is impoverished in detail and vividness (Raes et al., 2005; Williams et al., 2006; see also Williams et al., 2007) and more focused on the past than on the future (Ruby et al., 2013) and connected to reduced executive functioning, particularly cognitive flexibility (Davis & Nolen-Hoeksema, 2000).

Interestingly, the hippocampus seems to be a key structure in all those features. Engagement of the hippocampus in episodic memory has been shown to correlate with enrichment and vividness of the remembered or simulated episodes (Addis & Schacter, 2008; Eldridge et al., 2000;Lebreton et al., 2013) and hippocampal atrophy has been connected to impoverished episodic memory in different patient groups (Bergouignan, 2011, Thomann et al., 2012). hippocampal engagement seems to be also especially important for simulating future scenarios

(Addis, Wong & Schacter, 2007) and alterations of hippocampal activations have been shown to be pronounced during simulation of future states (Hach,Tippett &Addis, 2014)). Furthermore reduced volume in depression as well as the ablation of neurogenesis in animal models of depression is connected to cognitive flexibility (Frodl, Schaub & Banac, 2006; Burghardt et al., 2012; Garthe, Behr & Kempermann, 2009).

Moreover, deficits in episodic memory and cognitive flexibility seem to be altered by antidepressant treatment (Pehrson et al., 2014) and antidepressants have been shown to block the effect of unpredictable stress on cognitive flexibility in animal-models of depression (Bondi et al., 2008). Additionally, in a recent review of studies about the influence of antidepressants on resting state connectivity, Dichter, Smisk & Smoski (2014) found that the most coherent effect of antidepressants was an increase of the functional connectivity between frontal and limbic regions, highlighting the connectivity between those regions as a target of antidepressants.

However, important limitations of the study presented here are that no behavioral data were obtained, so that the behavioral consequences of hippocampal volume change are remaining rather speculative and that there has not been any control group, so that it is not possible to determine whether changes of the treatment are normalizing resting state activity or hippocampal volume. It is also important to point out that neurogenesis in the dentate gyrus has been shown to be important for the negative control of the hippocampus on the HPA-axis (Snyder, 2011) and that acute administration of cortisol has been shown to lead to impairments of autobiographical memory (Schlosser et al., 2010). Additionally, inducing an overgeneral-style of memory retrieval enhances the affective reactivity to stressful events (Philippot et al., 2003). Consequently there seems to be a reciprocal influence between stress and the DMN as well as stress and neurogenesis, which could be an important aspect to further understand the relationship between DMN and neurogensis. Structural changes in the hippocampus are however not a unique feature of depression (Sala et al., 2004) and antidepressant are not only effective in treating depression (Hollingworth, Burgess & Whiteford,2010).

However, the present study contributes to a growing body of research that neurogenesis and increasing volume of the hippocampus are important factors in the response to antidepressant treatment and while alterations of the hippocampus are hardly enough to explain the whole pic-

ture of depressive symptoms and also might be to unspecific for such an account, this findings are pointing to a role of structural alterations in the hippocampus as a factor in the chronicity of depression and maladjustment and stability of the depressive state (see also Holzheimer & Mayberg, 2011)

In summary there is converging evidence that functional and structural alterations in the hippocampus and the mediotemporal lobe as well as a dissociation of the mediotemporal subsytem of the DMN play important roles in the pathology of depression as well as are targets of treatment with antidepressants. The central finding of this study is that response to antidepressant treatment is connected to an increase of hippocampal volume, which is driven by changes in the CA3 and DG subfields and accompanied by a reintegration of the hippocampus in the DMN.

5 References

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia, 45(7), 1363–77. doi:10.1016/j.neuropsychologia.2006.10.016

Addis, D. R., & Schacter, D. L. (2008). Constructive episodic simulation: temporal distance and detail of past and future events modulate hippocampal engagement. Hippocampus, 18(2), 227–37. doi:10.1002/hipo.20405

Akers, K. G., Martinez-Canabal, A., Restivo, L., Yiu, A. P., De Cristofaro, A., Hsiang, H.-L. L., ... Frankland, P. W. (2014). Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science, 344(6184), 598–602. doi:10.1126/science.1248903

America Psychiatric Association (1994). Diagnostic and Statistic Manual of Mental Disorders. Washington: APA

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., ... Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biological Psychiatry, 57(10), 1079–88. doi:10.1016/j.biopsych.2005.02.021

Andersen, P., Morris, R., Amaral, D., Bliss, T., & O'Keefe, J. (2007). The hippocampus book. New York: Oxford Universtity Press

Andrews, G., Sanderson, K., Corry, J., & Lapsley, H. M. (2000). Using epidemiological data to model efficiency in reducing the burden of depression. The Journal of Mental Health Policy and Economics, 3(4), 175–186. doi:10.1002/mhp.96

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. Neuron, 65(4), 550–62. doi:10.1016/j.neuron.2010.02.005

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry, 18(3), 251–70. doi:10.1177/1073858411403316

Andrews-Hanna, J. R., Saxe, R., & Yarkoni, T. (2014). Contributions of episodic retrieval and mentalizing to autobiographical thought: evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. NeuroImage, 91, 324–35. doi:10.1016/j.neuroimage.2014.01.032

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Annals of the New York Academy of Sciences, 1316, 29–52. doi:10.1111/nyas.12360

Arnone, D., McKie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., ... Anderson, I. M. (2013). State-dependent changes in hippocampal grey matter in depression. Molecular Psychiatry, 18(12), 1265–72. doi:10.1038/mp.2012.150

Autry, A.E. & Monteggia, L.M. (2012). Brain-Derived Neurotrophic Factor and Neuropsychiatric Disorders. Pharmacological Review, 64(2),238-258.doi: 10.1124/pr.111.005108

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. Science, 319(5870), 1640–2. doi:10.1126/science.1152882

Baghai, T. C., Baldwin, D. S., Barrett, B., Baumann, P., Ghalib, K., Goodwin, G., ... Sartorius, N.(2007). Antidepressant medication and other treatment of depressive disorders: a CINP Task Force report based on a review of evidence. International Journal of Neuropsychopharmacology, 10, S1-S207. doi:10.1017/S1461145707008255

Bates, D., Maechler, M., & Bolker, B. (2013). lme4: Linear mixed-effects models using S4 classes. R package version 0.999999-2 .

Belzung, C., Willner, P., & Philippot, P. (2014). Depression: from psychopathology to pathophysiology. Current Opinion in Neurobiology, 30C, 24–30. doi:10.1016/j.conb.2014.08.013

Bergami, M., Rimondini, R., Santi, S., Blum, R., Götz, M., & Canossa, M. (2008). Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. Proceedings of the National Academy of Sciences, 105(40), 15570–15575. Retrieved from http://www.pnas.org/lookup/pmid?view=long&pmid=18832146

Bergouignan, L., Lefranc, J. P., Chupin, M., Morel, N., Spano, J. P., & Fossati, P. (2011). Breast cancer affects both the hippocampus volume and the episodic autobiographical memory retrieval. PloS One, 6(10), e25349. doi:10.1371/journal.pone.0025349

Bernal-Rusiel, J. L., Greve, D. N., Reuter, M., Fischl, B., & Sabuncu, M. R. (2012). Statistical analysis of longitudinal neuroimage data with Linear Mixed Effects models. NeuroImage, 66, 249–260. doi:10.1016/j.neuroimage.2012.10.065

Berman, M. G., Peltier, S., Nee, D. E., Kross, E., Deldin, P. J., & Jonides, J. (2011). Depression, rumination and the default network. Social Cognitive and Affective Neuroscience, 6(5), 548–55. doi:10.1093/scan/nsq080

Bessa, J. M., Ferreira, D., Melo, I., Marques, F., Cerqueira, J. J., Palha, J. A, ... Sousa, N. (2009). The mood-improving actions of

antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Molecular Psychiatry, 14(8), 764–73, 739. doi:10.1038/mp.2008.119

Binder, J., & Frost, J. (1999). Conceptual processing during the conscious resting state: a functional MRI study. Journal of Cognitive Neuroscience, 11(1), 80–93. Retrieved from http://www.mitpressjournals.org/doi/abs/10.1162/089892999563265

Blendy, J. (2006). The role of CREB in depression and antidepressant treatment. Biological Psychiatry, 59(12), 1144–50. doi:10.1016/j.biopsych.2005.11.003

Boldrini, M., Santiago, A. N., Hen, R., Dwork, A. J., Rosoklija, G. B., Tamir, H., … John Mann, J. (2013). Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 38(6), 1068–77. doi:10.1038/npp.2013.5

Bondi, C. O., Rodriguez, G., Gould, G. G., Frazer, A., & Morilak, D. a. (2008). Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 33(2), 320–31. doi:10.1038/sj.npp.1301410

Booij, L., Van der Does, A. J., & Riedel, W. J. (2003). Monoamine depletion in psychiatric and healthy populations: review. Molecular Psychiatry, 8, 951–973. doi:10.1038/sj.mp.4001423

Botteron, K.N., Raichle, M.E., Drevets, W.C., Heath, A.C., & Todd, R.D.(2002). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biological Psychiatry,51,342–344.doi: http://dx.doi.org/10.1016/S0006-3223(01)01280-X

Boubela, R. N., Huf, W., Kalcher, K., Sladky, R., Filzmoser, P., Pezawas, L., ...Windischberger, C., Moser, E. (2012). A highly parallelized framework for computationally intensive MR data analysis. Magma (New York, N.Y.), 25(4), 313–20. doi:10.1007/s10334-011-0290-7

Braun, U., Plichta, M. M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., ..,Meyer-Lindenberg, A. (2012). Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. NeuroImage, 59(2), 1404–12. doi:10.1016/j.neuroimage.2011.08.044

Bremner, J. D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., ...Charney, D. S. (2002). Reduced volume of orbitofrontal cortex in major depression. Biological Psychiatry, 51(4), 273–279. doi:10.1016/S0006-3223(01)01336-1

Brunoni, A. R., Lopes, M., & Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. The International Journal of Neuropsychopharmacology, 11(8), 1169–80. doi:10.1017/S1461145708009309

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. Annals of the New York Academy of Sciences, 1124, 1–38. doi:10.1196/annals.1440.011

Burghardt, N. S., Park, E. H., Hen, R., & Fenton, A. (2012). Adult-born hippocampal neurons promote cognitive flexibility in mice. Hippocampus, 22(9), 1795–808. doi:10.1002/hipo.22013

Cameron, H. A, & Glover, L. R. (2014). Adult Neurogenesis: Beyond Learning and Memory. Annual Review of Psychology, 66. doi:10.1146/annurev-psych-010814-015006

Campbell, S. , Marriott, M., Nahmias ,C., & MacQueen, G. M. (2004) Lower hippocampal volume in patients suffering from depression: a meta-analysis. American Journal of Psychiatry,161,598–607.doi: 10.1176/appi.ajp.161.4.598

Castrén, E. (2004). Neurotrophic effects of antidepressant drugs. Current Opinion in Pharmacology, 4(1), 58–64. doi:10.1016/j.coph.2003.10.004

Castrén, E. (2005). Is mood chemistry? Nature Reviews. Neuroscience, 6(3), 241–6. doi:10.1038/nrn1629

Castrén, E., & Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Developmental Neurobiology, 70(5), 289–97. doi:10.1002/dneu.20758

Castrén, E. (2013). Neuronal network plasticity and recovery from depression. JAMA Psychiatry, 70, 983–989. Retrieved from http://archpsyc.jamanetwork.com/article.aspx?articleID=1710491&utm_source=dlvr.it& utm _medium=twitter

Caetano, S. C., Kaur, S., Brambilla, P., Nicoletti, M., Hatch, J. P., Sassi, R. B., … Soares, J. C. (2006). Smaller cingulate volumes in unipolar depressed patients. Biological Psychiatry, 59(8), 702–706.doi : http://dx.doi.org/10.1016/j.biopsych.2005.10.011

Chao, M. V. (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. Nature Reviews. Neuroscience, 4(4), 299–309. doi:10.1038/nrn1078

Chen, G., Saad, Z. S., Britton, J. C., Pine, D. S., & Cox, R. W. (2013). Linear mixed-effects modeling approach to FMRI group analysis. NeuroImage, 73, 176–90. doi:10.1016/j.neuroimage.2013.01.047

Chisholm, D., Sanderson, K., Ayuso-Mateos, J. L., & Saxena, S. (2004). Reducing the global burden of depression: Population-level analysis of intervention cost-effectiveness in 14 world regions. The British Journal of Psychiatry, 184(5), 393–403. doi:10.1192/bjp.184.5.393

Christian, K. M., Song, H., & Ming, G. (2014). Functions and dysfunctions of adult hippocampal neurogenesis. Annual Review of Neuroscience, 37, 243–62. doi:10.1146/annurev-neuro-071013-014134.

Clelland, C., Choi, M., Romberg, C., Clemenson, G., Fragniere, A., Tyers, P., … Bussey, T. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science, 325(5937), 210–213. doi:10.1126/science.1173215.A

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., … Yang, T. T. (2013). Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. Biological Psychiatry, 74(12), 898–907. doi:10.1016/j.biopsych.2013.05.036

Coppen, A .(1967). The biochemistry of affective disorders. British Journal of Psychiatry, 113, 1237–1264. doi: 10.1192/bjp.113.504.1237

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews. Neuroscience, 3(3), 201–15. doi:10.1038/nrn755

Cox, R.W. (2012) AFNI: What a long strange trip it's been. NeuroImage, 62(2), 743-747.doi: 10.1016/j.neuroimage.2011.08.056

Cunha, C., Brambilla, R., & Thomas, K. L. (2010). A simple role for BDNF in learning and memory? Frontiers in Molecular Neuroscience, 3, 1–14. doi:10.3389/neuro.02.001.2010

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis. Frontiers in Human Neuroscience, 7(July), 372. doi:10.3389/fnhum.2013.00372

David, D., Samuels, B., Rainer, Q., Wang, J.-W., Marsteller, D., Drew, I. M. M., … Hen, R. (2009). Behavioral effects of fluoxetine in an animal model of anxiety/depression are mediated by both neurogenesis-dependent and independent mechanisms. Neuron, 62(4), 479–493. doi:10.1016/j.neuron.2009.04.017.BEHAVIORAL

Davis, R., & Nolen-Hoeksema, S. (2000). Cognitive inflexibility among ruminators and nonruminators. Cognitive Therapy and Research, 24(6), 699–711. Retrieved from http://link.springer.com/article/10.1023/A:1005591412406

De Kwaasteniet, B., Ruhe, E., Caan, M., Rive, M., Olabarriaga, S., Groefsema, M., … Denys, D. (2013). Relation between structural and functional connectivity in major depressive disorder. Biological Psychiatry, 74(1), 40–7. doi:10.1016/j.biopsych.2012.12.024

Deussing, J.M. (2006). Animal models of depression. Drug Discovery Today: Disease Models,3(4), 375-383. doi:10.1016/j.ddmod.2006.11.003

Dichter, G. S., Gibbs, D., & Smoski, M. J. (2014). A Systematic Review of Relations between Resting-State functional-MRI and Treatment Response in Major Depressive Disorder. Journal of Affective Disorders, 172, 8–17. doi:10.1016/j.jad.2014.09.028

Doucet, G., Naveau, M., Petit, L., Delcroix, N., Zago, L., Crivello, F., … Joliot, M. (2011). Brain activity at rest: a multiscale hierarchical functional organization. Journal of Neurophysiology, 105(6), 2753–63. doi:10.1152/jn.00895.2010

Duan, X., Kang, E., Liu, C. Y., Ming, G.-L., & Song, H. (2008). Development of neural stem cell in the adult brain. Current Opinion in Neurobiology, 18(1), 108–15. doi:10.1016/j.conb.2008.04.001

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, ...Weinberger, D. R. (2003). The BDNF val66met Polymorphism Affects Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function, 112, 257–269. Retrieved from http://www.sciencedirect.com/science/article/pii/S0092867403000357

Eichele, T., Debener, S., Calhoun, V. D., Specht, K., Engel, A. K., Hugdahl, K., … Ullsperger, M. (2008). Prediction of human errors by maladaptive changes in event-related brain networks. Proceedings of the National Academy of Sciences of the United States of America, 105(16), 6173–8. doi:10.1073/pnas.0708965105

Eisch, A. J., Bolaños, C. a, de Wit, J., Simonak, R. D., Pudiak, C. M., Barrot, M., … Nestler, E. J. (2003). Brain-derived neurotrophic factor in the ventral midbrain–nucleus accumbens pathway: a role in depression. Biological Psychiatry, 54(10), 994–1005. doi:10.1016/j.biopsych.2003.08.003

Eriksson,P. S.,Perfilieva,E.,Björk-Eriksson,T.,Alborn,A., Nordborg, C., Peterson, D.A., & Gage, F.H. (1998). Neurogenesis in the adult human hippocampus. Nature Medicine,4, 1313-1317.doi:10.1038/3305

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: a selective role

for the hippocampus during retrieval. Nature Neuroscience, 3, 1149–1152.doi:10.1038/80671

Fanselow, M. S., & Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? Neuron, 65(1), 7–19. doi:10.1016/j.neuron.2009.11.031

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron, 33(3), 341–55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11832223

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences of the United States of America, 102(27), 9673–8. doi:10.1073/pnas.0504136102

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews. Neuroscience, 8(9), 700–11. doi:10.1038/nrn2201

Frankland, P. W., Köhler, S., & Josselyn, S. A. (2013). Hippocampal neurogenesis and forgetting. Trends in Neurosciences, 36(9), 497–503. doi:10.1016/j.tins.2013.05.002

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Hohne,T., Banac, S., Schorr, ...Möller, H.J.(2004).Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. Journal of Clinical Psychiatry, 65,492–499.

Frodl, T., Schaub, A., & Banac, S. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. Journal of Psychiatry & Neuroscience : JPN, 31(5), 316–323. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1557684/

Frodl, T., Jäger, M., Smajstrlova, I., Born, C., Bottlender, R., Palladino, T., … Meisenzahl, E. M. (2008). Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. Journal of Psychiatry & Neuroscience : JPN, 33(5), 423–30.
Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2527720&tool=pmcentrez&rendertype=abstract

Fu, C. H. Y., Steiner, H., & Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiology of Disease, 52, 75–83. doi:10.1016/j.nbd.2012.05.008

Gao, W., & Lin, W. (2012). Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. Human Brain Mapping, 33(1), 192–202. doi:10.1002/hbm.21204

Garthe, A., Behr, J., & Kempermann, G. (2009). Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. PloS One, 4(5), e5464. doi:10.1371/journal.pone.0005464

Ge, S., Yang, C.-H., Hsu, K.-S., Ming, G.-L., & Song, H. (2007). A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron, 54(4), 559–66. doi:10.1016/j.neuron.2007.05.002

Golland, Y., Golland, P., Bentin, S., & Malach, R. (2008). Data-driven clustering reveals a fundamental subdivision of the human cortex into two global systems. Neuropsychologia, 46(2), 540–53. doi:10.1016/j.neuropsychologia.2007.10.003

Gotlib, I., & Joormann, J. (2010). Cognition and depression: current status and future directions. Annual Review of Clinical Psychology, 27(6), 285–312. doi:10.1146/annurev.clinpsy.121208.131305.Cognition

Gueorguieva, R., & Krystal, J.H. (2004). Move Over ANOVA: Progress in Analyzing Repeated-Measures Data. Archives of General Psychiatry, 61,310-317.doi:10.1001/archpsyc.61.3.310

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biological Psychiatry, 62(5), 429–37. doi:10.1016/j.biopsych.2006.09.020

Gruberger, M., Ben-Simon, E., Levkovitz, Y., Zangen, A., & Hendler, T. (2011). Towards a neuroscience of mind-wandering. Frontiers in Human Neuroscience, 5, 56. doi:10.3389/fnhum.2011.00056

Grønli, J., Bramham, C., Murison, R., Kanhema, T., Fiske, E., Bjorvatn, B., ... Portas, C.M. (2006). Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper. Pharmacology, Biochemistry, and Behavior 85, 842–849. doi:10.1016/j.pbb.2006.11.021

Hach, S., Tippett, L. J., & Addis, D. R. (2014). Neural changes associated with the generation of specific past and future events in depression. Neuropsychologia, 65, 41–55. doi:10.1016/j.neuropsychologia.2014.10.003

Hamilton J.P., Siemer M., & Gotlib I.H. (2008). Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Molecular Psychiatry,13, 993–1000.doi: 10.1038/mp.2008.57

Hamilton, J. P., Chen, G., Thomason, M. E., Schwartz, M. E., & Gotlib, I. H. (2011a). Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Molecular Psychiatry, 16(7), 763–72. doi:10.1038/mp.2010.46

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011b). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biological Psychiatry, 70(4), 327–33. doi:10.1016/j.biopsych.2011.02.003

Hamilton, J. P., Chen, M. C., & Gotlib, I. H. (2013). Neural systems approaches to understanding major depressive disorder: an intrinsic functional organization perspective. Neurobiology of Disease, 52, 4–11. doi:10.1016/j.nbd.2012.01.015

Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry, 23, 56–62. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC495331/

Hassabis, D., Kumaran, D., Vann, S. D., & Maguire, E. A. (2007). Patients with hippocampal amnesia cannot imagine new experiences. Proceedings of the National Academy of Sciences of the United States of America, 104(5), 1726–31. doi:10.1073/pnas.0610561104

Hoffman, L., & Rovine, M. J. (2007). Multilevel Models for the Experimental Psychologist: Foundations and Illustrative Examples.Faculty Publications, Department of Psychology. Paper 421.http://digitalcommons.unl.edu/psychfacpub/421

Holm, S. (1979) A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics, 6, 65–70. Retrieved from http://www.jstor.org/stable/4615733

Hollingworth, S. A., Burgess, P. M., & Whiteford, H. A. (2010). Affective and anxiety disorders: prevalence, treatment and antidepressant medication use. The Australian and New Zealand Journal of Psychiatry, 44(6), 513–9. doi:10.3109/00048670903555138

Holtzheimer, P. E., & Mayberg, H. S. (2011). Stuck in a Rut: Rethinking Depression and its Treatment. Trends in Neuroscience, 34 (1), 1-9. doi: 10.1016/j.tins.2010.10.004.Stuck

Horch, H. W., & Katz, L. C. (2002). BDNF release from single cells elicits local dendritic growth in nearby neurons. Nature Neuroscience, 5 (11),1177-1184.doi:10.1038/nn927

Hox J. J. (2010). Multilevel analysis. Techniques and applications. (2th ed.). New York:Routledge

Jo, H., Saad, Z., Simmons, W., Milbury, L., & Cox, R. (2010). Mapping sources of correlation in resting state FMRI, with artifact detection and removal. Neuroimage, 52(2), 571–582. doi:10.1016/ j.neuroimage.2010 .04.246.Mapping

Karpova, N. N., Pickenhagen, A., Lindholm, J., Tiraboschi, E., Kulesskaya, N., Agústsdóttir, A., ... Castrén, E. (2011). Fear erasure in mice requires synergy between antidepressant drugs and extinction training. Science, 334(6063), 1731–4. doi:10.1126/science.1214592

Katz, M. M., Bowden, C. L., & Frazer, A. (2010). Rethinking depression and the actions of antidepressants: uncovering the links between the neural and behavioral elements. Journal of Affective Disorders, 120(1-3), 16–23. doi:10.1016/j.jad.2009.08.011

Kempermann, G., Kuhn, H. G., & Gage, F. H. (1997). More hippocampal neurons in adult mice living in an enriched environment. Nature, 386(6624), 493–5. doi:10.1038/386493a0

Kheirbek, M. A., Klemenhagen, K. C., Sahay, A., & Hen, R. (2012). Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nature Neuroscience, 15(12), 1613–20. doi:10.1038/nn.3262

Kheirbek, M., Tannenholz, L., & Hen, R. (2012). NR2B-dependent plasticity of adult-born granule cells is necessary for context discrimination. The Journal of Neuroscience, 32(25), 8696–8702. doi:10.1523/JNEUROSCI.1692-12.2012.NR2B-dependent

Kheirbek, M., Drew, L., & Burghardt, N. (2013). Differential control of learning and anxiety along the dorsoventral axis of the dentate gyrus. Neuron, 77(5), 955–968. doi:10.1016/j.neuron.2012.12.038.Differential

King, M. J., Macdougall, A. G., Ferris, S., Herdman, K. A, & McKinnon, M. C. (2011). Episodic simulation of future events is impaired in patients with major depressive disorder. Psychiatry Research, 187(3), 465–7. doi:10.1016/j.psychres.2011.02.002

Lagace, D. C., Donovan, M. H., DeCarolis, N. A, Farnbauch, L., Malhotra, S., Berton, O., ...Eisch, A. J. (2010). Adult hippocampal neurogenesis is functionally important for stress-induced social avoidance. Proceedings of the National Academy of Sciences of the United States of America, 107(9), 4436–41. doi:10.1073/pnas.0910072107

LaHuis, D. M., & Ferguson, M. W. (2007). The Accuracy of Significance Tests for Slope Variance Components in Multilevel Random

Coefficient Models. Organizational Research Methods, 12(3), 418–435. doi:10.1177/1094428107308984

Lavergne, F., & Jay, T. M. (2010). A new strategy for antidepressant prescription. Frontiers in Neuroscience, 19(4), 192. doi: 10.3389/fnins.2010.00192

Lebreton, M., Bertoux, M., Boutet, C., Lehericy, S., Dubois, B., Fossati, P., & Pessiglione, M. (2013). A critical role for the hippocampus in the valuation of imagined outcomes. PLoS Biology, 11(10), e1001684. doi:10.1371/journal.pbio.1001684

Leech, R., Kamourieh, S., Beckmann, C. F., & Sharp, D. J. (2011). Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31(9), 3217–24. doi:10.1523/JNEUROSCI.5626-10.2011

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. Brain : A Journal of Neurology, 137, 12–32. doi:10.1093/brain/awt162

Leutgeb, J. K., Leutgeb, S., Moser, M.-B., & Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science, 315(5814), 961–6. doi:10.1126/science.1135801

Li, Y., Luikart, B., Birnbaum, S., Chen, J., Kwon, C.-H., Kernie, S., ...Parada, L. (2008). TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron, 59(3), 399–412. doi:10.1016/j.neuron.2008.06.023.TrkB

Lopez-Munoz, F., & Alamo, C. (2009). Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s Until Today. Current Pharmaceutical Design, 15(14), 1563–1586. doi:10.2174/138161209788168001

Lu, B., Pang, P.T. & Woo, N.H. (2005). The yin and yang of neurotrophin action. Nature Review Neuroscience, 6(8), 603-614.doi:10.1038/nrn1726

Luo, Y., Cao, Z., Wang, D., Wu, L., Li, Y., Sun, W., & Zhu, Y. (2014). Dynamic study of the hippocampal volume by structural MRI in a rat model of depression. Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 35(11), 1777–83. doi:10.1007/s10072-014-1837-y

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Molecular Psychiatry, 16(3), 252–64. doi:10.1038/mp.2010.80

Malberg, J. E., Eisch, a J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 20(24), 9104–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11124987

Marazziti, D., Consoli, G., Picchetti, M., Carlini, M., & Faravelli, L. (2010). Cognitive impairment in major depression. European Journal of Pharmacology, 626(1), 83–6. doi:10.1016/j.ejphar.2009.08.046

Marr, D. (1971). Simple memory: a theory for archicortex. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 262(841), 23–81. Retrieved from http://www.jstor.org/stable/2417171

Mateus-Pinheiro, A., Pinto, L., Bessa, J. M., Morais, M., Alves, N. D., Monteiro, S., … Sousa, N. (2013). Sustained remission from depressive-like behavior depends on hippocampal neurogenesis. Translational Psychiatry, 3, e210. doi:10.1038/tp.2012.141

Maya-Vetencourt, J. F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., Castren, E., & Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science, 320,385–388.doi: 10.1126/science.1150516

Mayberg, H.S.(1997). Limbic-cortical dysregulation: a proposed model of depression. Journal of Neuropsychiatry and Clininical Neuroscience 9 (3), 471–481.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., … Tzourio-Mazoyer, N. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. Brain Research Bulletin, 54(3), 287–298. Retrieved from http://www.sciencedirect.com/science/article/pii/S0361923000004378

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. Journal of Affective Disorders, 119(1-3), 1–8. doi:10.1016/j.jad.2009.04.022

McEwen, B. S. (2005). Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism: Clinical and Experimental, 54, 20–3. doi:10.1016/j.metabol.2005.01.008

McEwen, B., Chattarji, S., & Diamond, D. (2010). The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Molecular Psychiatry, 15(3), 237–249. doi:10.1038/mp.2009.80.The

Mirescu, C., & Gould, E. (2006). Stress and adult neurogenesis. Hippocampus, 16(3), 233–8. doi:10.1002/hipo.20155

Molteni, R., Calabrese, F., Cattaneo, A., Mancini, M., Gennarelli, M., Racagni, G., & Riva, M. A. (2009). Acute stress responsiveness of the neurotrophin BDNF in the rat hippocampus is modulated by chronic treatment with the antidepressant duloxetine. Neuropsychopharmacology, 34(6), 1523-1532.doi: 10.1038/npp.2008.208.

Monteggia, L. M., Barrot, M., Powell, C. M., Berton, O., Galanis, V., Gemelli, T., ... Nestler, E. J. (2004). Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proceedings of the National Academy of Sciences of the United States of America, 101(29), 10827–32. doi:10.1073/pnas.0402141101

Montgomery, S. A., & Asberg, M. A (1979). New Depression Scale Designed to be Sensitive to Change. British Journal of Psychiatry, 134, 382-389. doi: 10.1192/bjp.134.4.382

Nakashiba, T., Cushman, J. D., Pelkey, K. A, Renaudineau, S., Buhl, D. L., McHugh, T. J., ... M. S.,Tonegawa, S. (2012). Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell, 149(1), 188–201. doi:10.1016/j.cell.2012.01.046

Nejad, A. B., Fossati, P., & Lemogne, C. (2013). Self-referential processing, rumination, and cortical midline structures in major depression. Frontiers in Human Neuroscience, 7(October), 666. doi:10.3389/fnhum.2013.00666

Nestler, E. J., Barrot, M.,DiLeone, R.J., Eisch, A. J.,Gold, S. J., Monteggia, L.M. (2002). Neurobiology of depression. Neuron, 34, 13–25.doi:10.1016/S0896-6273(02)00653-0

Neto, F. L., Borgesa, G. ,Torres-Sanchez, S., Micob, J.A., & Berrocosob, E. (2011). Neurotrophins Role in Depression Neurobiology: A Review of Basic and Clinical Evidence. Current Neuropharmacology, 9, 530-552. doi: 10.2174/157015911798376262

Nibuya, M., Nestler, E., & Duman, R. (1996). Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. The Journal of Neuroscience, 76(7), 2365–2372.
Retrieved from http://www.jneurosci.org/content/16/7/2365.short

Nich,C., & Carrol, K. (1997). Now You See It, Now You Don't A Comparison of Traditional Versus Random-Effects Regression Models in the Analysis of Longitudinal Follow-Up Data From a Clinical Trial. Journal of Consulting and Clinical Psychology, 65 (2), 252 -261. doi:http://dx.doi.org/10.1037/0022-006X.65.2.252

Niibori, Y., Yu, T.-S., Epp, J. R., Akers, K. G., Josselyn, S. & Frankland, P. W. (2012). Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. Nature Communications, 3, 1253. doi:10.1038/ncomms2261

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking Rumination. Perspectives on Psychological Science, 3(5), 400–424. doi:10.1111/j.1745-6924.2008.00088.x

Parihar, V., Hattiangady, B., & Kuruba, R. (2011). Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. Molecular Psychiatry, 16(2), 171–183. doi:10.1038/mp.2009.130.Predictable

Park, H., & Poo, M. (2013). Neurotrophin regulation of neural circuit development and function. Nature Reviews. Neuroscience, 14(1), 7–23. doi:10.1038/nrn3379

Pehrson, A. L., Leiser, S. C., Gulinello, M., Dale, E., Li, Y., Waller, J., & Sanchez, C. (2014). Treatment of cognitive dysfunction in major depressive disorder-a review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetin. European Journal of Pharmacology, doi:10.1016/j.ejphar.2014.07.044

Perera, T. D., Coplan, J. D., Lisanby, S. H., Lipira, C. M., Arif, M., Carpio, C., ... Dwork, A. J. (2007). Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 27(18), 4894–901. doi:10.1523/JNEUROSCI.0237-07.2007

Petrik, D., Lagace, D. C., & Eisch, A. J. (2012). The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? Neuropharmacology, 62(1), 21–34. doi:10.1016/j.neuropharm.2011.09.003

Philippot, P., Schaefer, A., & Herbette, G. (2003). Consequences of specific processing of emotional information: Impact of general versus specific autobiographical memory priming on emotion elicitation. Emotion, 3(3), 270–283. doi:http://dx.doi.org/10.1037/1528-3542.3.3.270

Pinheiro, J. C., & Bates, D. M. (2000). Mixed-Effects Models in S and S-PLUS, New York: Springer.

Pinheiro, J. C., Bates, D. M., DebRoy, S., & Sarkar, D. (2013). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-113.

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacol-

ogy 33, 88–109.doi:10.1038/sj.npp.1301574

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P., Martin, D., … Loo, C. K. (2013). Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 38(11), 2101–8. doi:10.1038/npp.2013.126

Poldrack, R., Mumford, J., & Nichols, T. (2011). Handbook of functional MRI data analysis. New York: Cambridge University Press.

Posternak, M. A., & Zimmerman, M. (2007). Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials. British Journal of Psychiatry, 190(287-292). doi:1 0.0.1192/92/bjp.b p.106.028028555

R Development Core Team (2013). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, http://www.R-project.org.

Raes, F., Hermans, D., Williams, J. M. G., Demyttenaere, K., Sabbe, B., Pieters, G., & Eelen, P. (2005). Reduced specificity of autobiographical memory: a mediator between rumination and ineffective social problem-solving in major depression? Journal of Affective Disorders, 87(2-3), 331–5. doi:10.1016/j.jad.2005.05.004

Reichardt, L. F. (2006). Neurotrophin-regulated signalling pathways. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 361(1473), 1545–64. doi:10.1098/rstb.2006.1894

Reuter, M., Schmansky, N. J., Rosas, H.D., & Fischl, B. (2012). Within-Subject Template Estimation for Unbiased Longitudinal Image Analysis. Neuroimage, 61(4),1402-1418. doi: 10.1016/j.neuroimage.2012.02.084

Reuter, M., & Fischl, B., (2011). Avoiding asymmetry-induced bias in longitudinal image processing. Neuroimage, 57 (1), 19-21. doi: 10.1016/j.neuroimage.2011.02.076

Rossi, C., Angelucci, A., Costantin, L., Braschi, C., Mazzantini, M., Babbini, F., … Caleo, M. (2006). Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. The European Journal of Neuroscience, 24(7), 1850–6. doi:10.1111/j.1460-9568.2006.05059.x

Roy, M., Shohamy, D., & Wager, T. D. (2012). Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends in Cognitive Sciences, 16(3), 147–56. doi:10.1016/j.tics.2012.01.005

Ruby, F. J. M., Smallwood, J., Engen, H., & Singer, T. (2013). How self-generated thought shapes mood–the relation between mind-wandering and mood depends on the socio-temporal content of thoughts. PloS One, 8(10), e77554. doi:10.1371/journal.pone.0077554

Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. Nature Reviews. Neuroscience, 14(9), 609–25. doi:10.1038/nrn3381

Saarelainen, T., Hendolin, P., Lucas, G., Koponen, E., Sairanen, M., Macdonald, E., … Castre, E. (2003). Activation of the TrkB Neurotrophin Receptor Is Induced by Antidepressant Drugs and Is Required for Antidepressant-Induced Behavioral Effects, 23(1), 349–357.

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M., Burghardt, N. S., … Hen, R. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature, 472(7344), 466–70. doi:10.1038/nature09817

Sairanen, M., Lucas, G., Ernfors, P., Castrén, M., & Castrén, E. (2005). Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. Journal of Neuroscience, 25(5), 1089-1094.doi: 10.1523/JNEUROSCI.3741-04.2005

Sala, M., Perez, J., Soloff, P., Ucelli di Nemi, S., Caverzasi, E., Soares, J. C., & Brambilla, P. (2004). Stress and hippocampal abnormalities in psychiatric disorders. European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 14(5), 393–405. doi:10.1016/j.euroneuro.2003.12.005

Sambataro, F., & Wolf, N. (2013). Default mode network in depression: a pathway to impaired affective cognition? Clinical Neuropsychiatry, 10(5), 212–216. Retrieved from http://www.clinicalneuropsychiatry.org/pdf/sambataro_web.pdf

Sambataro, F., Wolf, N. D., Pennuto, M., Vasic, N., & Wolf, R. C. (2014). Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. Psychological Medicine, 44, 2041–2051. doi:10.1017/S0033291713002596

Samuels, B. A, & Hen, R. (2011). Neurogenesis and affective disorders. The European Journal of Neuroscience, 33(6), 1152–9. doi:10.1111/j.1460-9568.2011.07614.x

Santarelli, L., Saxe, M., Gross, C., & Surget, A. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science, 301, 805–809. Retrieved from http://www.sciencemag.org/content/301/5634/805.short

Scharfman, H., Goodman, J., Macleod, A., Phani, S., Antonelli, C., & Croll, S. (2005). Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Experimental Neurology, 192(2), 348–56. doi:10.1016/j.expneurol.2004.11.016

Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., & Szpunar, K. K. (2012). The future of memory: remembering, imagining, and the brain. Neuron, 76(4), 677–94. doi:10.1016/j.neuron.2012.11.001

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: a review of supporting evidence. American Journal of Psychiatry, 122, 509–522. DOI: 10.1176/ajp.122.5.509

Schermuly I., Wolf, D., Lieb, K., Stoeter, P., & Fellgiebel, A. (2011). State dependent posterior hippocampal volume increases in patients with major depressive disorder. Journal of Affective Disorders 135,405–409.doi: 10.1016/j.jad.2011.07.017

Schinder, A. F., & Poo, M. (2000). The neurotrophin hypothesis for synaptic plasticity. Trends in Neuroscience ,23, 639–645.doi : http://dx.doi.org/10.1016/S0166-2236(00)01672-6

Schlosser, N., Wolf, O. T., Fernando, S. C., Riedesel, K., Otte, C., Muhtz, C., ... Wingenfeld, K. (2010). Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls. Psychoneuroendocrinology, 35(2), 316–20. doi:10.1016/j.psyneuen.2009.06.015

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ...Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 27(9), 2349–56. doi:10.1523/JNEUROSCI.5587-06.2007

Sen, S., Duman, R., & Sanacora, G. (2008). Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biological Psychiatry, 64(6), 527–32. doi:10.1016/j.biopsych.2008.05.005

Shirayama, Y., Chen, A. C.-H., Nakagawa, S., Russell, D. S., & Duman, R. S. (2002). Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 22(8), 3251–61. doi:20026292

Shulman, G., Fiez, J., & Corbetta, M. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. Journal of Cognitive Neuroscience,9 (5) , 648–663. Retrieved from http://www.mitpressjournals.org/doi/abs/10.1162/jocn.1997.9.5.648

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S.R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biological Psychiatry 61 (2), 198–209. doi: http://dx.doi.org/10.1016/j.biopsych.2006.05.048

Singh, K. D., & Fawcett, I. P. (2008). Transient and linearly graded deactivation of the human default-mode network by a visual detection task. NeuroImage, 41(1), 100–12. doi:10.1016/j.neuroimage.2008.01.051

Smallwood, J., & Andrews-Hanna, J. (2013). Not all minds that wander are lost: the importance of a balanced perspective on the mind-wandering state. Frontiers in Psychology, 4(441), 1–6. doi:10.3389/fpsyg.2013.00441

Smith, M., & Makino, S. (1995). Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. The Journal of Neuroscience, 15(3), 1768–1777. Retrieved from http://www.jneurosci.org/content/15/3/1768.short

Snapinn, S.N., & Jiang, Q. (2007). Responder analyses and the assessment of a clinically relevant treatment effect. Trials, 8(3), http://www.trialsjournal.com/content/8/1/31.

Snijder, T., & Bosker, R.J. (2011). Multilevel Analysis: An Introduction to basic and advanced multilevel modeling. London: Sage.

Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature, 476(7361), 458–61. doi:10.1038/nature10287

Spalding,K.L., Bergmann,O.,Alkass, K., Bernard, S., Salehpour,M.,Huttner,H. B., ... Frise, J.(2013). Dynamics of Hippocampal Neurogenesis in Adult Humans. Cell, 153, 1219-1227.doi: 10.1016/j.cell.2013.05.002.

Spreng, R., Mar, R., & Kim, A. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. Journal of Cognitive Neuroscience, 21(3), 489–510. Retrieved from http://www.mitpressjournals.org/doi/abs/10.1162/jocn.2008.21029

Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., & Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. NeuroImage, 53(1), 303–17. doi:10.1016/j.neuroimage.2010.06.016

Spreng, R., & Sepulcre, J. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. Journal of Cognitive Neuroscience, 25(1), 1–19. doi:10.1162/jocn

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences of the United States of America, 105(34), 12569–74. doi:10.1073/pnas.0800005105

St-Laurent, M., Moscovitch, M., Jadd, R., & McAndrews, M. P. (2014). The perceptual richness of complex memory episodes is compromised by medial temporal lobe damage. Hippocampus, 24(5), 560–76. doi:10.1002/hipo.22249

Summerfield, J. J., Hassabis, D., & Maguire, E. A. (2009). Cortical midline involvement in autobiographical memory. NeuroImage, 44(3), 1188–200. doi:10.1016/j.neuroimage.2008.09.033

Surget, A., Saxe, M., Leman, S., Ibarguen-Vargas, Y., Chalon, S., Griebel, G., Hen, R. & Belzung, C. (2008) Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biological Psychiatry, 64, 293–301.doi: 10.1016/j.biopsych.2008.02.022

Surget, A., Tanti, A., Leonardo, E. D., Laugeray, A., Rainer, Q., Touma, C., … Belzung, C. (2011). Antidepressants recruit new neurons to improve stress response regulation. Molecular Psychiatry, 16(12), 1177–88. doi:10.1038/mp.2011.48

Taliaz, D., Stall, N., Dar, D. E., & Zangen, A. (2010). Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Molecular Psychiatry, 15(1), 80–92. doi:10.1038/mp.2009.67

Tanti, A., Belzung, C. (2013). Hippocratic neurogenesis: a biomarker for depression or antidepressant effects? Methodological considerations and perspectives for future research.Cell Tissue Research ,354, 203 -219. doi:10.1007/s00441-013-1612-z

Thomann, A. P., Seidl, U., Brinkmann, J., Hirjak, D., Traeger, T., Christian Wolf, R., … Schroder, J. (2012). Hippocampal Morphology and Autobiographic Memory in Mild Cognitive Impairment and Alzheimer's Disease. Current Alzheimer Research, 9(4), 507–515. doi:10.1002/hipo.1077

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., … Fava, M. (2006). Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice, 163(1), 28–40. doi: 10.1176/appi.ajp.163.1.28

Tulving, E. (2002). Episodic memory: from mind to brain. Annual Review of Psychology, 53, 1–25. doi:10.1146/annurev.psych.53.100901.135114

Uddin, L. Q., Kelly, a M., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Human Brain Mapping, 30(2), 625–37. doi:10.1002/hbm.20531

Van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 20(8), 519–34. doi:10.1016/j.euroneuro.2010.03.008

Van Leemput, K., Bakkour, A., Benner, T., Wiggins, G., Wald, L. L., & Augustinack, J. (2009). Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. Hippocampus, 19, 549–557. doi: 10.1002/hipo.20615

Veer, I. M., Beckmann, C. F., van Tol, M.-J., Ferrarini, L., Milles, J., Veltman, D. J., … Rombouts, S. a R. B. (2010). Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Frontiers in Systems Neuroscience, 4(41), 1–10. doi:10.3389/fnsys.2010.00041

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. Journal of Neurophysiology, 100(6), 3328–42. doi:10.1152/jn.90355.2008

Vythilingam, M., Vermetten, E., Anderson, G. M., Luckenbaugh, D., Anderson, E. R., Snow, J., … Bremner, J. D. (2004). Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biological Psychiatry, 56(2), 101–12. doi:10.1016/j.biopsych.2004.04.002

Weisz, V. I., & Argibay, P. F. (2012). Neurogenesis interferes with the retrieval of remote memories: forgetting in neurocomputational terms. Cognition, 125(1), 13–25. doi:10.1016/j.cognition.2012.07.002

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. Annual Review of Clinical Psychology, 8, 49–76. doi:10.1146/annurev-clinpsy-032511-143049

Williams, J. M. G., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., & Dalgleish, T. (2007). Autobiographical memory specificity and emotional disorder. Psychological Bulletin, 133(1), 122–48. doi:10.1037/0033-2909.133.1.122

Williams, J. M. G., Eelen, P., Raes, F., & Hermans, D. (2006). Reduced autobiographical memory specificity and affect regulation. Cognition

& Emotion, 20(3-4), 402–429. doi:10.1080/02699930500341003

Willner, P., Scheel-Krüger, J., & Belzung, C. (2013). The Neurobiology of depression and antidepressant action. Neuroscience and Biobehavioural Review. http://dx.doi.org/ 10.1016/j.neubiorev.2012.12.007

World Health Organization (2012). Depression a global public health concern.
www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf

Wu, M. V, & Hen, R. (2014). Functional dissociation of adult-born neurons along the dorsoventral axis of the dentate gyrus. Hippocampus, 24(7), 751–61. doi:10.1002/hipo.22265

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., … Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of Neurophysiology, 106(3), 1125–65. doi:10.1152/jn.00338.2011

Young, K. D., Erickson, K., Nugent, A. C., Fromm, S. J., Mallinger, A. G., Furey, M. L., & Drevets, W. C. (2012). Functional anatomy of autobiographical memory recall deficits in depression. Psychological Medicine, 42(2), 345–57. doi:10.1017/S0033291711001371

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., & Gong, Q. (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biological Psychiatry, 70(4), 334–42. doi:10.1016/j.biopsych.2011.05.018

Zhao, C., Teng, E. M, Summers, R. G.,Ming G. L., & Gage, F. H. (2006). Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus,The Journal of Neuroscience, 26, 3–11.doi: 10.1523/JNEUROSCI.3648-05.2006

Zhou, Y., Yu, C., Zheng, H., Liu, Y., Song, M., Qin, W., … Jiang, T. (2010). Increased neural resources recruitment in the intrinsic organization in major depression. Journal of Affective Disorders, 121(3), 220–30. doi:10.1016/j.jad.2009.05.029

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biological Psychiatry, 71(7), 611–7. doi:10.1016/j.biopsych.2011.10.035

Name: Julian Provenzano
Geburtsdatum: 10.02.1987

2008-2015 Diplomstudium Universtiät Wien

2012 Auslandsemester University of Oslo

2006 Abitur